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AUSTRALASIAN ANNALS OF MEDICINE

Journal of The Royal Australasian College of Physicians

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NOTICE TO CONTRIBUTORS

AUSTRALASIAN ANNALS OF MEDICINE is intended for the publication of original observations and research in internal medicine and the medical sciences in general by medical graduates and other scientific workers.

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AUSTRALASIAN ANNALS OF MEDICINE

VOLUME I NOVEMBER 1952 NUMBER 2

THE PATTERN OF DISEASE IN CHILDHOOD[1]

SIR MACFARLANE BURNET
Walter and Eliza Hall Institute of Medical Research, Melbourne

I AM honoured by your invitation to deliver the fourth Charles Clubbe Memorial Oration, though I am very conscious that my knowledge of pædiatrics is of the slightest. Clubbe himself is but a name to me except insofar as the accounts of previous orators have conveyed something of his personality and achievement. He was one of those men, I gather, who by their qualities come to dominate their own medical field and determine its local traditions. His interests in pædiatrics were surgical, humanitarian and administrative, and it would have been more appropriate if I could have chosen some topic more akin in spirit to his own broad human interests. I must, however, confine myself to an outsider's view of one important phase of pædiatrics, infectious disease in childhood, and I am taking as my theme for this lecture the broad significance of age on the incidence and outcome of infectious disease.

It is common knowledge that in any stable community each of the main infectious diseases has its own characteristic pattern of incidence. In ordinary times the acute bacterial infections of the meninges are diseases of infancy, while primary infection with the virus of *herpes simplex* is commonest between one and three years. Measles and chicken-pox, diphtheria and poliomyelitis all tend to be most frequent in early school age. In women there is a peak of susceptibility to tuberculosis between twenty and twenty-five years, while psittacosis rarely produces serious symptoms in people aged under forty years. In recent years the mortality from influenza has been heavily concentrated on the old, though in 1918–1919 the great pandemic killed almost selectively those in the prime of life.

Such differences in age incidence have always interested epidemiologists, and in recent years there has been special interest in the way poliomyelitis has changed in the sixty odd years of its history as an epidemic disease. The infantile paralysis of the beginning of the century was almost limited to children aged under five years. Present-day poliomyelitis is alarming us with the large number of severe cases in young adults. My own interest in the subject has very largely centred on this changing incidence of poliomyelitis, which I have discussed on several previous occasions. In this lecture I should like to discuss more broadly the physiological and immunological factors which contribute to the patterns of the incidence and mortality of infectious disease.

The raw material for any discussion of age incidence must be found in published computations, which are derived in the last analysis from the stated opinion of some person, normally a doctor, that a certain individual was at a given time suffering from the disease in question or had died from it. Two very important practical difficulties arise here. The first is the validity of the diagnosis. Some diseases like measles and mumps are so uniform in their appearance that we can be certain that at least 90% of the stated diagnoses are correct. There are other diseases—for example, psittacosis, "Q" fever and atypical pneumonia—in which an ætiological diagnosis is impossible without laboratory study. In such a group useful figures for age incidence would be obtainable only from such series of patients as had been

[1] The fourth Charles Clubbe Memorial Oration delivered in the Great Hall of the University of Sydney on September 25, 1952.

adequately tested. Poliomyelitis represents an intermediate condition. Clinical diagnosis of paralytic poliomyelitis is relatively straightforward, but it is the modern view that the clinical disease can be due to any one of three antigenically distinct types of virus. What we measure in standard epidemiological studies on poliomyelitis is essentially the behaviour of Brunhilde type virus infections with, in many instances, just enough poliomyelitis due to the Lansing and Leon types to leave the edges of the picture a little blurred.

The second difficulty, also classically exemplified by poliomyelitis, is where the line is to be drawn between the clinical case to be reported and the subclinical or near subclinical case which is not reported. It is known to every practitioner that when an epidemic of poliomyelitis is about many non-paralytic infections are reported, probably correctly, as poliomyelitis, which in the absence of an epidemic would never be reported at all. Essentially the same difficulty exists for every disease—and this includes the great majority—in which there is a complete range of symptomatic expression from nil to fatal infection; diphtheria and tuberculosis are to hand as outstanding examples. The difficulty is not very important from our present point of view unless age has a major influence in determining the clinical severity of first contact with infection. In general a practical measure is to compare in such cases the age incidence of death from the disease with the age incidence of reported cases. The dissociation of the two curves will give an index of the influence of age in modifying the severity of the disease.

In studying the age incidence of disease it is convenient and for many forms of comparison essential to represent the figures in some form of graph. A block histogram showing the percentage of cases or deaths falling in each five-year period is the type most commonly used. However, when interest is concentrated on the diseases of infancy or childhood this is a most inconvenient method. I have spent a good deal of effort in trying various alternative methods, and I have adopted for this lecture a method which has not to my knowledge been previously used for the purpose. It is based essentially on ideas put forward many years ago by the French physiologist Lecomte du Noüy in a semi-popular monograph called "Biological Time" (1936).

Du Noüy was associated with Carrel's investigations on the treatment of wounds during the first World War, and his ideas of biological time as contrasted with ordinary commonsense clock time were an outcome of studies on the rate of healing of wounds. He found that there were certain regularities in the process, and as other people had noticed in a rough way before him, he found that wounds healed more rapidly in young soldiers than in older men. Bodily processes seemed to move at a more rapid *tempo* for the twenty-year-old than for the man of fifty. Seeking a mathematical relationship between age and the rate of healing of wounds, he found that to a reasonable approximation the rate was proportional to the reciprocal of the patient's age. In other words, if a child of ten years healed with a rate equal to 10, the corresponding rates for twenty, forty and fifty years would be found from the

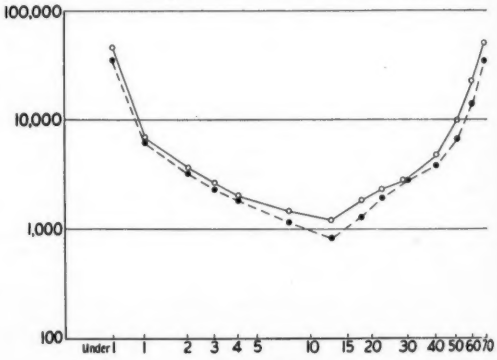


FIGURE I.
Over-all mortality at various ages: Australia, 1931–1940. Males, open circles, continuous line; females, black circles, interrupted line. (Lancaster, 1951.) Abscissæ: logarithmic age scale.

the ratio 1/10 : 1/20 : 1/40 : 1/50—that is, 10 : 5 : 2·5 : 2. One could express the situation as indicating that the "physiological duration" of any given year (or other unit) of life was proportional to the fraction that year represented of the total life so far experienced. This can be very conveniently shown by taking the beginning of life as the moment of fertilization, so that birth is regarded as taking place at an age of 0·75 year, and plotting conventional ages from 0 to seventy years on a logarithmic scale between 0·75 year and 70·75 years. Nearly all the curves I shall show with this lecture are plotted with this time scale and the numbers or percentages of cases or deaths are also plotted as ordinates on a logarithmic scale.

In Figure I there are shown curves of overall mortality at various ages from the first year of life to the decade sixty-five to seventy-four years. These form almost symmetrical curves high at each end and reaching a minimum at the age period ten to fifteen years. We shall be concerned almost entirely with the first period

of the curve, from birth till the child reaches the prime of life, which medically if not socially is at the ages of ten to twelve years. In all probability in using a logarithmic time scale we are trying to compensate for the progressive slowing down of developmental processes that goes on from conception to maturity. It is probable that there are variations in the rate of this deceleration at different periods, and it may be that the correct scale would be one which made allowance for these—a scale, for instance, which would give a straight line for the development of weight with age. As shown in Figure II, this curve is hardly a straight line on this particular grid. However, all that we require

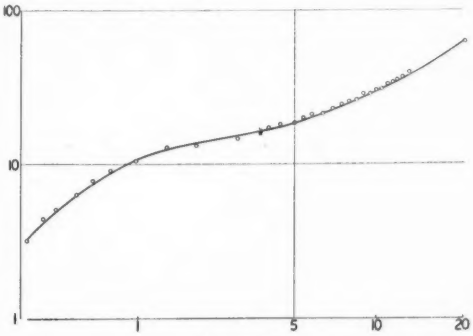


FIGURE II.
Development of weight with age, logarithmic age scale. Weight in kilograms (ordinates) shown logarithmically. (Data from Illingworth, 1950.)

is some means of depicting the facts that will make clear the preponderating importance in regard to infectious disease of the first years of life.

I shall make only brief reference to the changes in the reaction of adults of different ages to infection ; but if this line of thought is followed there is much to be said for changing over at maturity, say between twenty and thirty years, to a linear time scale. However, in all except two of the graphs I have used the logarithmic scale over the whole period.

With occasional exceptions fatal infections do not occur in immune individuals, and in discussing the general features of age incidence curves it is convenient to consider first those conditions in which immunity phenomena are not concerned. A study of the case fatality of a few such diseases in relation to age provides some important indications.

For obvious reasons we can deal only with case fatality rates effectively where we are concerned with diseases of well-defined ætiology and not highly variable in their virulence over the area and the time being considered. We are in practice confined to the reportable infectious diseases, except where a special study has been made of a large number of cases of some rarer condition of special interest.

In Figure III there are shown curves of case fatality in relation to age taken from British

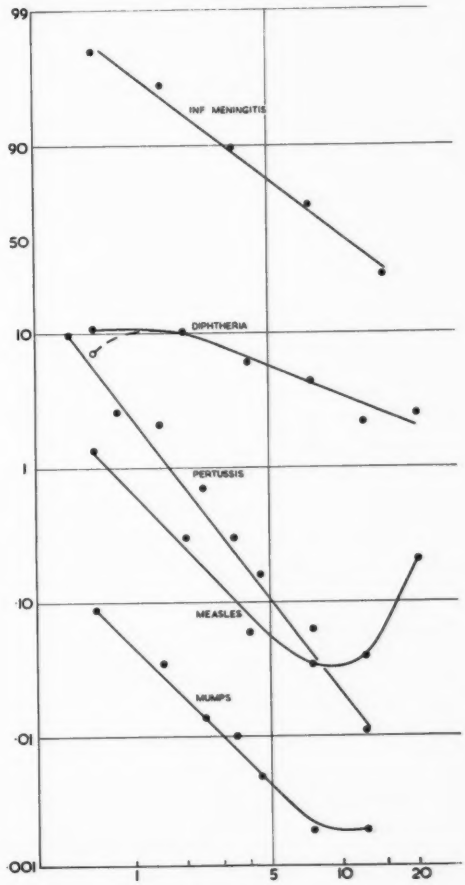


FIGURE III.
Case fatality by age of several childhood infections. Ordinates: logarithmic percentage scale. Abscissæ: logarithmic age scale. Data from the following sources: influenzal meningitis, Dolphin and Popham (1951); pertussis, Dauer (1943); diphtheria and measles, Registrar-General (1949); mumps, Collins (1929).

and American experience of the common childhood diseases and in addition of influenza bacillus meningitis. The latter is added as an example of a highly lethal condition, the figures for which are from investigations made before any effective treatment for the disease was available. It is evident that on this double logarithmic method of plotting all the curves show a rather striking approach to a straight

line over most of the period of childhood. There are moderate differences from one set of figures to another, depending probably on such factors as completeness of reporting and criteria for diagnosis as well as the effectiveness of treatment. However, the general character for each disease is recognizable in all of them. The slope is closely similar for pertussis and measles, for the highly fatal influenzal meningitis and, curiously enough, for the trivial mortality from mumps. The corresponding curves for

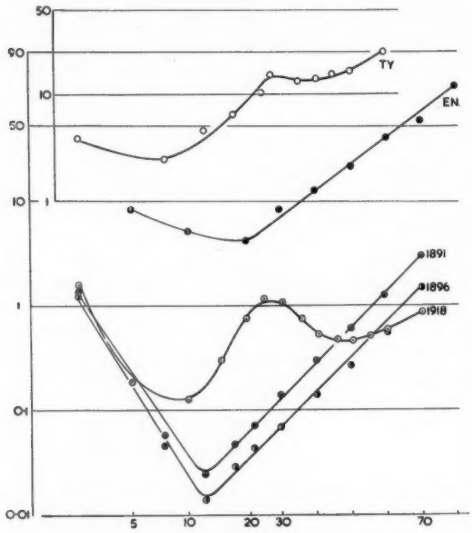


FIGURE IV.

Case fatality rates by age for diseases predominantly of adult life. Ordinates : logarithmic percentage scale. Time scale changes from logarithmic to linear at twenty-five years. "TY", typhoid fever in Western Australia, 1912. "EN", St. Louis encephalitis, 1933. Three bottom curves show respiratory deaths in England and Wales for the years shown. Data obtained as follows : respiratory infections and influenza, 1891, 1896, 1918, Ministry of Health Report (1920) ; typhoid fever, Cumpston and McCallum (1927) ; St. Louis encephalitis, 1935, Report on the St. Louis outbreak of encephalitis, U.S. Public Health Bulletin Number 214.

scarlet fever and diphtheria differ in showing a less rapid fall with increasing age. There is no significant mortality from pertussis over the age of ten years, but measles and scarlet fever show a well marked increase in mortality during adolescence, more marked in males than in females.

There are two groups of infections which were once the most important of all causes of death — gastro-intestinal infections and respiratory tract infections. Even now they are still of major significance at both ends of life. Both sorts of infection are due to a wide variety of bacteria, most of which may be more or less commonly found in healthy individuals. Close study of any single patient will often make it possible to say that some specific microorganism was responsible for that infection ; but the vast mass of the deaths reported under either heading are of persons who were not studied bacteriologically. In both groups the numbers of possible pathogenic species are so wide that it may be legitimate and helpful to look at the mortality from respiratory infections as the case fatality of a composite disease, from which everyone suffers every year, and which produces no immunity that matters. An exactly similar point of view may be taken in regard to deaths from gastro-intestinal infection.

Consideration of these two groups of non-immunizing infections necessarily brings the changes associated with maturity and old age into the picture. Although it is not strictly relevant to a discussion of childhood diseases, it is very desirable to look at two important patterns of mortality in adult life. In Figure IV are shown the case fatality rates at different ages for Saint Louis encephalitis and typhoid fever and the mortality rate by ages for respiratory infections in two peak influenza years (1891 and 1918) and a year without an influenza epidemic (1896), the figures being taken from experience in England and Wales. In this figure the time scale is logarithmic to thirty years, but linear from twenty years onwards ; that is, the interval corresponding to twenty to thirty years is given the value appropriate to the logarithmic scale used from birth onward. This value is then arbitrarily taken as that for each subsequent decade, so that having regard to the wide age intervals used the scale can be said to be logarithmic to thirty years and linear from twenty years onwards. This brings out more clearly the regularity of the change with age.

Through the kindness of Dr. H. O. Lancaster, I have been able to obtain Australian figures for mortality from respiratory infections broken down into one-year age groups in the childhood period. These figures have been expressed graphically in Figure V, the same convention being used as to time scale. It will be seen that over both the pre-adult (logarithmic) and the adult (linear) periods, the approach of the two straight lines is inescapable.

Simple inspection of these curves suggests strongly that the following four main factors are operating :

1. There is a non-specific increase in resistance to the general damaging effect of infections, over the period from birth to the age of ten to twelve years. This increased resistance may

well be due to some single factor varying regularly with physiological age.

2. The increasing resistance may be partially overcome by the specific damaging effects of the diphtheria bacillus or the scarlet fever streptococcus.

3. With the onset of adolescence a new factor inducing a progressive increase in susceptibility appears. In the case of the childhood diseases

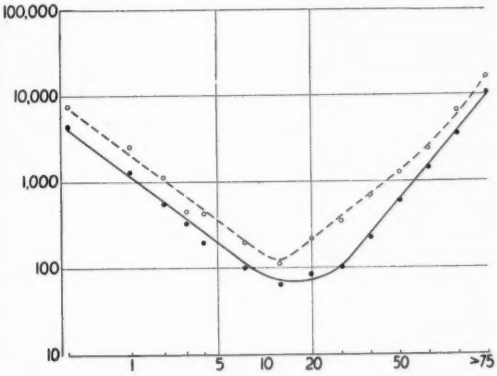


FIGURE V.

The age incidence of mortality (deaths per million *per annum*) from respiratory infections. Interrupted line, males. Continuous line, females. Age scale changes from logarithmic to linear at twenty-five years. Data from Australian figures for 1908–1910, 1941–1945, provided by Dr. H. O. Lancaster.

it is hard to establish the point at which this susceptibility of adult life reaches its maximum. There is much to suggest, however, that the same effect was responsible for the characteristic shape of the mortality curve from respiratory infection in 1918–1919. The important features of the curves are the peak about twenty-five to thirty years and the greater incidence of fatality on men than on women. There is incomplete evidence that this holds also for measles and poliomyelitis in non-immune groups.

In Figure VI are plotted figures from a detailed survey of influenza in 1918–1919 in Baltimore. There are shown (i) the incidence of symptomatic infection—that is, any febrile infection not otherwise diagnosed that was sufficient to send the patient to bed, (ii) the incidence of pneumonia, and (iii) the incidence of death. We could, I think, also add a fourth curve, a straight line running at 100% to indicate that probably every person in the community must have been infected by the virus at one time or another during the pandemic period. This figure provides a good example of how the curve of age incidence of a disease will vary according to the criteria used for diagnosis on report.

4. Finally there is the well known increase in the lethal quality of infectious disease when it attacks the elderly and the old; this is represented by the straight line curve shown for several conditions in Figure IV. There are a few diseases which produce virtually no serious illness in persons aged under forty years; psittacosis and the 1933 outbreak of Saint Louis encephalitis in the city of that name are the best known. A striking recent example of concentration of mortality on the old was given by the experience of influenza in Liverpool in 1951. The mortality in the worst week of this epidemic was actually higher than in the worst weeks of 1918–1919, but deaths were almost limited to people aged over fifty-five years (Semple, 1951).

An examination of these and many similar curves suggests very strongly that, irrespective of the specific nature of the disease, there are three basic patterns of mortality. When uncomplicated by special features of the disease they give the following effects: (i) The straight line fall of mortality from birth onwards may be called the effect of Factor I. (ii) Factor II is responsible for the "young adult" mortality shown most clearly in pandemic influenza.

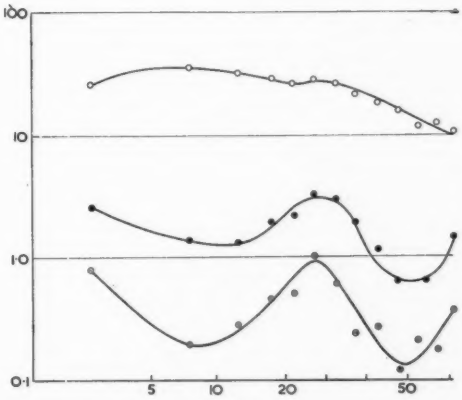


FIGURE VI.

Age incidence of influenza in Baltimore, 1918–1919, showing the incidence (as percentage of the total population studied) of symptomatic infection (top line), of pneumonia (centre line) and of death (bottom line). Data from Vaughan (1922).

(iii) The progressive rise in mortality with age once childhood is past is ascribed to Factor III.

I cannot escape the conviction that these three factors will eventually be capable of statement each in terms of some unitary physiological principle. It is a very different matter to attempt to state the nature of those principles at the present time. I can do no

more than make some suggestions as to the possible lines along which such principles might be sought.

Factor I will be one of the greatest interest to pædiatricians. The effect of this factor is evident in such a wide range of conditions—gastro-enteritis, pertussis and influenzal meningitis, for example—that it must be expressible in the broadest possible terms. I should suggest that the initially high and rapidly diminishing susceptibility of the infant to death from infective processes of such varying character is related to the changing capacity to withstand and compensate for disturbances in homœostasis.

Growth is a continuous and amazingly complex process. Perhaps it is legitimate to separate in thought three aspects of that indivisible whole, the four dimensional continuum of the growing human organism from conception to birth, childhood and maturity. There is first the morphological aspect, the process by which the fertilized ovum segments and folds, grows and differentiates into the specialized organs of the child and adult. The second is the development of neuro-muscular function from the simple reflexes and uncoordinated limb movements of the infant to effective muscular action and speech, to acceptance of a social pattern and to all the manifold ways in which a human personality can flower to distinction or degenerate. The third aspect, the only one that concerns us directly, is the development of effective homœostatic mechanisms. The healthy older child or young adult has an almost limitless capacity to maintain his internal environment, blood plasma, and intercellular and intracellular fluids, in the state needed for the most effective functioning of the body. Temperature, pH, partial pressure of oxygen, viscosity, colloid osmotic pressure, leucocyte count and dozens of other variables are maintained constant or appropriately changed to fulfil the varying requirements of the body as a whole. This effectiveness of internal pattern and control is as much a product of growth and experience-through-function as the skills of a trapeze artist, an orchestra conductor or a statesman.

There are two primary biological mysteries: one is the replication of molecular pattern by which gene produces gene and virus gives rise to other virus, each after its kind. The second is the unifying control that ensures that at every stage from the ovum to maturity there is an effective organism adapted to the standard environment and activities of the period. It is a control that covers each of the aspects I have mentioned, morphological, neuro-mental and what we may call regulatory. I am concerned only with the last of these. The others are mentioned merely to make it easier to visualize the process by which control of homœostasis becomes firmer and more effectively related to bodily requirements as the child develops.

Behind everything is the predestined pattern on which the whole being must develop. In the process of reaching maturity the details of the pattern are filled in by the exercise of various functions called for by the environment. In the earliest stages there is a rapid movement from the absolutely sheltered environment of the uterus to less and less sheltered modes of life. Control of the internal environment must become progressively more efficient, and to do so it must progressively meet and deal with the type of events that can exercise the regulatory function. A child must walk before it can run—equally an infant must learn by contact with a variety of harmless or lowly virulent microorganisms what is needed to overcome more dangerous invaders. The high mortality from infection in infancy is to be ascribed essentially to failure of an adequately developed regulatory function to compensate for the changes induced by infection. In a discussion of these matters with Dr. John Perry, pathologist to the Children's Hospital in Melbourne, he gave as an interesting example of the difficulty of compensation in the infant the relative inefficiency of chloramphenicol in alleviating the symptoms of Salmonella enteritis in children compared with its effectiveness in removing the pathogen from the bowel. Once the normal balance has been disturbed, it is not sufficient simply to remove the initiating cause for the balance to be reestablished. An example from the experimental field is the extreme susceptibility of aseptically reared chickens to bacterial infection. It has been possible to raise chickens in a completely sterile environment. The grown birds, however, succumbed to acute generalized infection when injected with a culture of *B. subtilis*, which is completely innocuous to normal chicks.

Our interpretation of Factor I, then, is simply that mechanisms of homœostasis in the broadest sense need time and experience within their limitations, to develop. The fatal infection is the one which, coming too early, presses one or other of these mechanisms beyond its limitations.

The significance of the " young-adult " peak of mortality has been ascribed to Factor II. There is no doubt whatever about the reality of the phenomenon and its more active manifestation in males than in females. I have suggested elsewhere (Burnet, 1940) that there are two ways of looking at it. One is to adopt a frankly teleological attitude (call it an evolutionary point of view if you like), and consider what in a primitive human community would best serve the need for survival. Under such circumstances all endemic diseases would have been experienced before children reached the age of puberty and immunity established. In later life the major danger from micro-organismal invasion would be by way of infected wounds and abrasions. There is much in favour of the view that a rapid inflammatory reaction can be advantageous in leading to the speedy clearing up and repair of a superficial local infection. It is even clearer that a reaction which may be salutary in a localized region can be dangerous or lethal when it involves the whole body or most of some essential organ. We may look at the undue reactivity of the young adult, then, on the one hand as an adaptation to deal effectively with local infections, and on the other as a danger to his life when a generalized infection to which in Nature's view he " ought " to be immune, afflicts him. The second complementary line of approach is at the physiological level. Anyone with experience in skin testing for sensitization by such agents as killed virus suspensions will have observed that positive reactions in children are weaker and require larger doses to elicit them than in adults. There is an increased tissue reactivity to damage in young adults, possibly representing greater facility in the liberation of histamine and other pharmacologically active substances from damaged cells. The question of modified " allergic " reactivity is relevant here, but it would occupy too much space to merit discussion.

In summary Factor II is interpreted in terms of the more intense inflammatory reaction in the young adult, a response valuable in superficial infections, but positively dangerous when generalized infections occur in a non-immune adult.

Factor III has no place in a discussion on childhood disease, but it represents in some ways Factor I in reverse. The increasing vulnerability of old age is again a manifestation of inadequacy of response ; but instead of the unbalanced excessively labile situations provoked in the infant, or the " logical " but often excessive response in the young adult, we have a steadily progressing slowness and insufficiency of response.

In all this discussion of the three hypothetical factors it will be only too obvious that the general terms I have used give no indication of the nature of any isolated quantitative element responsible for the regularity of the change of case fatality with age.

So far we have been concerned only with the outcome of infection once it has been established. In the strict sense we have not been concerned at all with the incidence of infection or even with the age incidence of mortality. Only when incidence is virtually uniform over all age groups as in pandemic influenza can we use the overall incidence of death as a measure of the case fatality.

There are three main factors which determine the age incidence of reportable infection : first the influence of age on opportunity to be infected, secondly the changing ratio with age of clinical to subclinical infections, and thirdly the influence of past infection, clinical or subclinical, in providing specific immunity against reinfection. There is a fourth factor whose importance is harder to assess, but which cannot be neglected : this is the development with age of non-specific resistance to the initiation of infection.

In the actual findings with any given disease we shall usually find some evidence of the influence of all these factors. We may take measles first as the simplest of all infectious diseases to understand. For all practical purposes we can say (i) that there is no variation in the infectivity of different strains of measles virus, (ii) that subclinical infections do not occur, (iii) that every case is due to contact with another clinical case, and (iv) that once infected the person concerned is subsequently immune to measles.

Most infections will obviously occur when the first child of the family starts to mingle with other children, most commonly in his first years at school. He will bring infection home and younger members of the family will also be infected. With the standard modern family of two children separated by an interval of two years, the age incidence will differ significantly from that characteristic of the large family era. In particular there will be fewer cases in infants and hence a lower mortality. Some children will miss infection at the normal period, and it was very characteristic of the 1914–1918 war to find a relatively high incidence with a significant death rate amongst troops in camp. Once a child leaves primary school

there will be relatively few opportunities for him to become infected—the likely occasions are when he is mobilized for military service or when his own children being measles home to him. In a survey of common diseases in the United States it is interesting that mumps,

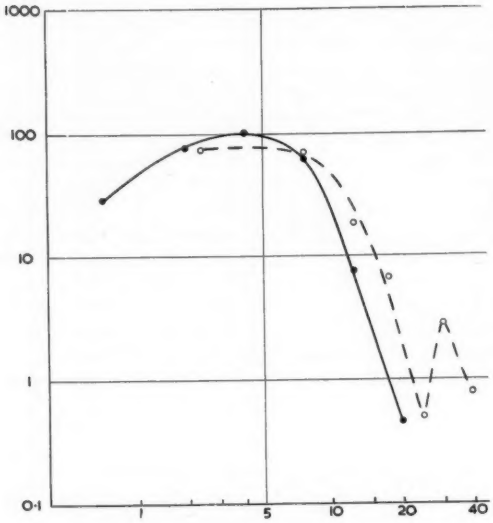


FIGURE VII.
Age incidence of measles. Closed circles, England and Wales (Registrar-General, 1949). Open circles, United States of America (Collins, 1935).

measles and chicken-pox all show a minor peak between twenty-five and thirty-five years (Figure VII). This almost certainly represents infectious disease brought back to the parents from the school.

The other childhood diseases show a rather similar pattern of incidence to measles, and there is nothing to be gained by discussing the patterns shown by chicken-pox, mumps and scarlet fever. Diphtheria is more important, since it is the classical example of the importance of subclinical infection.

The most satisfactory data on the development of immunity to diphtheria are to be found in Zingher's studies on the percentage of "Schick-positive" individuals at various ages in New York city during the early 1920's. I can find no other set of figures dealing with large enough numbers of individuals and expressed in small enough age groups to allow the calculation of the yearly incidence of immunizing infections. In Figure VIII the uppermost line indicates the proportions of the community at different ages who are susceptible to infection. This is taken directly from Zingher's figures. The next line shows the percentage changing from "Schick-positive" to "Schick-negative" in each year. This may be regarded for all practical purposes as the age incidence of subclinical infection, and as would be expected, it gives a curve similar in all essentials to that for measles. On the same diagram there is shown the age incidence of clinical diphtheria (as reported from New York city about the same period). The distance between the lines B and A indicates on a logarithmic scale the proportion of subclinical to clinical attacks. It will be seen that in children of two to four years subclinical infections seem to be proportionately more common than clinical infections, a finding of great interest in relation to the results with poliomyelitis.

The most interesting of all infectious diseases from the point of view of its age incidence is poliomyelitis. Everyone is aware of how it has changed in character from the literal "infantile paralysis" of the early years of this century to a

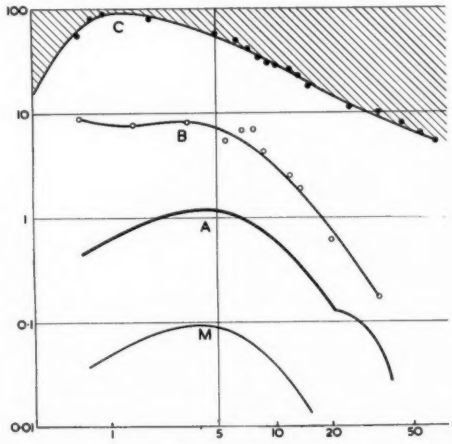


FIGURE VIII.
The age incidence of immunization and clinical infection by the diphtheria bacillus. Figure constructed from Zingher's (1923) data on Schick reactions and from annual reports of New York City Health Department (1920–1923) for incidence of reported disease. A, Age incidence of reported diphtheria, New York City (1921). B, Incidence of immunizing infections calculated from Zingher's data shown directly in curve C. M, Mortality in New York over the same period. Ordinates, percentage of population. Age scale logarithmic.

disease involving mostly children of school age with an increasing proportion of adults.

If we take first case-fatality rates, the values given for these in different investigations will obviously vary greatly according to the criterion used for diagnosing and reporting a case of poliomyelitis. The available curves are, how-

ever, all of the same general shape. Infants show a higher rate than young children, and there is a fairly steady rise in the case fatality rate with age. Cases over the age of forty years are so rare that one cannot be certain whether the curve should show a definite " young adult peak " or would continue upward with increasing age.

There is a general uniformity in the shape of the age incidence curves, a typical example of which can be seen in Figure IX, which shows the figures for the great New York epidemic of 1916. There is a peak of incidence at two to three years, and then from three to four years onward there is a steep descent that forms a virtual straight line with insignificant numbers of cases over the age of forty years. The steepness of this descending slope varies with the epidemic, the steepest being associated with epidemics in large urban communities with low living standards. The most interesting recent example is probably the 1942–1943 epidemic in Malta.

I think that we can now accept without hesitation the view that the whole epidemiology of poliomyelitis is controlled by immunological factors. I shall assume that any infection with a poliomyelitis virus, clinical or subclinical, gives rise to a long-lasting immunity against infection by virus of that type, and that the three types of poliomyelitis virus immunize each only against its own type. On this basis we can state that the form of the curves of age incidence is determined essentially by the degree of subclinical immunization to which the community has been exposed during the years preceding the epidemic.

In almost all the epidemics whose figures are available, once a certain age is passed (the particular age varying with the type of community), the case incidence falls on an approximate straight line by our present method of plotting the figures. Too much should not be read into this regularity. In essence it probably means that in each unit of time a constant proportion of those not immune at the beginning of the period become immune at the end of it. If intensity of exposure and susceptibility to infection did not change with age, the curve would be a straight line with a linear time scale. The better fit with a logarithmic scale may be due to the influence of one or more of several factors affecting either the past prevalence of immunizing infection or the epidemic of clinical disease on which the figures are based. The observed deviation from what might be expected could be due to (*a*) an increasing non-specific resistance to the initiation of an immunizing infection, or (*b*) to diminished exposure to infection during n[illegible] epidemic periods of the older age groups; if the deviation is related to the clinical epidemic being reported, the factors may be (*c*) that immunity resulting from past infection tends to become less effective in the older age groups, or (*d*) that the non-specific resistance increasing with age (*a* above) is much less evident with invasive strains of poliomyelitis virus than with non-invasive immunizing strains.

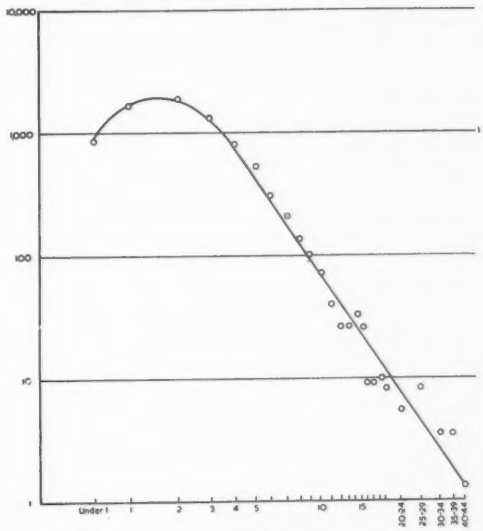


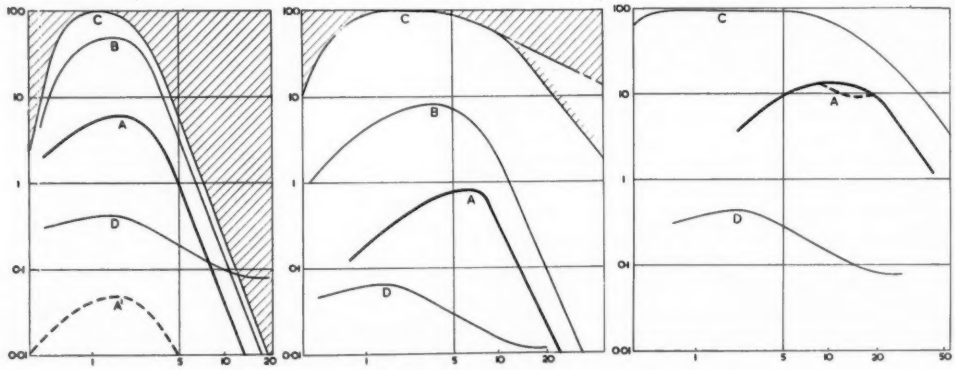
FIGURE IX.
The age incidence of poliomyelitis in the New York City epidemic of 1916. Data from International Committee (1932).

In Figures X, XI and XII I have attempted to illustrate the epidemiological situation responsible for three characteristic types of poliomyelitis outbreaks. The examples taken are Malta (1942–1943) as an epidemic occurring in a heavily immunized community, Melbourne (1937), a severe epidemic in an average Western community, and Saint Helena (1946), which is regarded as a " virgin soil " epidemic. The graphs are based upon and constructed around the reported age incidence of cases, but all the other lines are derived by a series of assumptions which at the present time appear reasonable but cannot claim universal acceptance. The first assumption is that the general immunological status of the community does not vary from year to year. Irrespective of the invasiveness (paralysis-producing power) of the current strain in any particular year, the numbers and age distribution of the persons infected and immunized are approximately the same.

The second major assumption is that the ratio of subclinical to clinical infections varies consistently with age, being approximately 10 times higher for children of two years than for persons of fifteen to twenty years, the absolute value of the ratio being of course dependent on the invasiveness of the strain concerned. The third assumption based on evidence from similar communities is that in Malta a 50% immunization level was reached at three years and that in Melbourne the 50% level was reached at eleven years, while in Saint Helena it is assumed that none of the population had ever been infected by poliomyelitis virus of the type responsible for the 1946 epidemic. In the Malta epidemic graph it is obvious that all significant happenings are complete by the age of ten years. In the other two communities it seems impossible to give a reasonable interpretation of the picture without assuming that from about the age of fifteen years onward there is a non-immunological increase in resistance to the initiation of infection. This may be a false interpretation; other factors which would act in the same sense are an unsuspectedly high exposure of the population to infection in past years, or some circumstance which removes older persons from the likelihood of infection in the epidemic being considered.

It should be stressed that these formulations of the epidemiological situation are guesses based on analogy and limited data. It is one of the great potentialities opened up by the new work on tissue culture of poliomyelitis virus that we should be able within a few years to obtain the data needed to construct a definitive picture of this kind for each serological type of virus.

This is not a lecture on poliomyelitis, and I must necessarily omit a great many points relevant to the age incidence observed in different times and places. What should be stressed is that in any disease producing large numbers of subclinical infections the observed age incidence of the clinical disease depends on the intensity of the infection moving through the community. The more active its movement, the lower will be the age incidence. In the case of poliomyelitis the characteristic relationship between age and the ratio of subclinical to clinical infections also ensures in general that the more thoroughly a population is saturated with the virus, the lower will be the overt incidence of disease. This in a nutshell is the justification for making every effort to find an effective form of immunization against the disease.



FIGURES X, XI and XII.

Diagrams to illustrate the epidemiological situation for three types of poliomyelitis epidemic. X. Malta, 1942–1943. XI. Melbourne, 1937. XII. St. Helena, 1947. Ordinates: Percentage of persons involved at each age, logarithmic scale. Abscissæ: logarithmic age scale. The smoothed curves are: A, Age incidence of reported cases. Actual data. B, Age incidence of all immunizing infections during epidemic period. C, Percentage of non-immunes by age groups at beginning of epidemic. D, To indicate changing ratio of subclinical/clinical infections with age. Data for Malta, 1942–1943, from Seddon *et alii* (1945), for Melbourne, 1937, from Dale (1938), for St. Helena, from Nissen (1947).

With these examples of measles, diphtheria and poliomyelitis before us we may attempt a more systematic statement of the factors governing the age incidence of overt infectious disease.

The first broad differentiation may be made between non-endemic and endemic diseases, or more explicitly between infections due to microorganisms which are likely to be encountered only under unusual circumstances and those due to pathogens or potential pathogens almost certain to be met by everyone. The difference is not absolute, and any division of infections into the two groups can be valid only

for the time and country for which it is made. And there are borderline cases — in our own community tuberculosis is diminishing so rapidly that it can hardly now be regarded as an endemic disease.

We are dealing with the incidence of recognized and reported disease. It will be obvious that before a case can be recognized two requirements must be fulfilled: (*a*) the patient must have contact with the specific pathogen, and (*b*) recognizable symptoms must be produced after infection is initiated. In special investigations we may be concerned with subclinical infections detectable only by laboratory tests, but in general there must be recognizable symptomatic expression of the infection before it becomes available for report, enumeration and study.

Opportunity for infection may be almost the only factor concerned in determining the age incidence of some non-endemic diseases. There are few such infections in Australia, but "Q" fever may be mentioned as an example in which clinical infection is almost limited to adults associated with abattoirs work or other aspects of the meat trade. In cases of this sort the observed age incidence is simply a reflex of the age composition of workers in the industry concerned.

Opportunity, of course, also plays its part in determining the incidence of the common infections. The major effect of a rising standard of living and the development of the hygiene of infancy and childhood has been to defer the age of first contact with most infections. In our own community this has been most striking in regard to tuberculosis. In the early days of the von Pirquet reaction it was said that almost all children had been infected with tuberculosis before they were fourteen years old. Now among the girls entering on their training as nurses in Melbourne less than 25% give a positive Mantoux reaction. In the same way any disease for which effective preventive measures are developed and applied shows a change in age incidence as it becomes progressively rarer.

With those infections which have remained ubiquitous, opportunity for contact still remains important, but we are more concerned with the complex possibilities that follow initiation of infection. We can regard every type of infection as having four potential aspects: (i) initial infection, in a tissue exposed in one way or another to the environment from which the microorganism is received; (ii) spread to other parts of the body in which lesions and symptoms may be manifested; (iii) generalized infection with corresponding symptoms; and (iv) antibody production which more or less effectively brings the infection to an end and prevents symptomatic infection in future. Any or all of these aspects may be involved in determining the age incidence of a given disease. In the broadest terms we may say that the age at which first contact with a given pathogen occurs will influence the symptomatic outcome in one of two ways. At certain ages the microorganism for one reason or another may be unable to initiate infection, so that neither symptoms nor immunity results. In the second place age will influence the symptomatic expression of any infection that is initiated. This can be put in other words by saying that the ratio of clinical to subclinical infections is characteristically modified by age. Where immunity is substantial or complete, the apparent age incidence will depend essentially on the rate with which the population is immunized by subclinical and clinical infections taken together.

I. NON-IMMUNOLOGICAL RESISTANCE TO THE INITIATION OF INFECTION

There is a good deal of evidence that as tissues age they become non-specifically resistant to the effective implantation of certain pathogens. *Pemphigus neonatorum*, staphylococcal infection of unbroken or only very slightly damaged skin, is hardly seen except in newborn infants. Primary *herpes simplex* is characteristically a disease of toddlers between the ages of one and three years. Anyone who reaches adult life free from herpetic infection is unlikely to be infected, although there must be constant opportunities for occasional virus particles to reach the mouth. If the incidence of secondary cases of diphtheria in a family is studied in relation to "Schick-positive" or "Shick-negative" status, it is found that "Schick-positive" children are much more liable to infection that "Schick-positive" adults. The physiological basis of this resistance may be in part related to greater epithelialization of skin and mucous membranes producing a mechanical barrier to infection, in part to the greater efficacy of a variety of clearing mechanisms.

The possibility of a reversed age effect must also be considered. It is striking that *B. abortus* infections are virtually never reported in children under five years, even where milk is known to be heavily infected. This phenomenon has been little studied in human beings, but it is known that young calves are not symptomatically infected nor do they produce antibody

when inoculated with cultures of the organism. As far as I am aware there are also no records of "Q" fever or psittacosis in young children. All three diseases have some curious common features, but the evidence on the aspects with which we are concerned is so slight that no more than this passing reference would be justified.

II. The Influence of Age on the Severity of Infection Once it Has Been Initiated: The Ratio of Subclinical to Clinical Infection

In discussing the effect of age on the severity of infection it must be clearly understood that any statements made must always be qualified with the phrase "other things being equal". In any given instance we can be certain that the outcome of infection is influenced by the virulence of the infecting strain, by the dose received, by the genetic constitution of the individual concerned and by environmental factors, notably climate. Nevertheless, when we are dealing with large communities the multitude of such variables is evened out in the statistical material, and we can see clear evidence of the part played by age as such.

The problem of the ratio between clinical and subclinical infections has been most frequently discussed in terms of poliomyelitis, which represents perhaps rather a special case. In several discussions on the epidemiology of poliomyelitis I have given the evidence for believing that in primary infections the lowest ratio of paralytic to non-paralytic infection is found in infancy, and that the ratio increases at least to the age of fifteen years and probably beyond. In other diseases it is hard to obtain relevant figures, and the influence of passive maternal immunity on infections in the first year is hard to assess. Perhaps the best approach to a valid generalization is to say that in the young child an infection will frequently produce a trivial short-lasting illness which in the non-immune young adult produces an outspoken clinical disease. In endemic areas of typhus, scrub typhus and typhoid fever, and to some extent at least yellow fever, childhood infections are inconspicuous, though probably most of them could be diagnosed if full diagnostic laboratory facilities were available.

In addition to poliomyelitis there are other members of the important group of infections in which the difference between clinical and subclinical manifestation depends on whether or not the infection passes from the tissue or site of initial infection to a vulnerable organ, most frequently the brain or meninges. One of the most clear-cut of these is influenza bacillus meningitis. Figure XIII includes the age incidence of all cases reported to 1948, and the case fatality according to age (*a*) before the introduction of specific therapy in 1937, and (*b*) between 1937 and 1948 under various combinations of sulphadiazine, streptomycin and specific antiserum therapy. It will be seen that the likelihood of meningeal infection falls more steeply than the case fatality. Here we have almost certainly two factors concerned, one an increasing resistance to the passage of

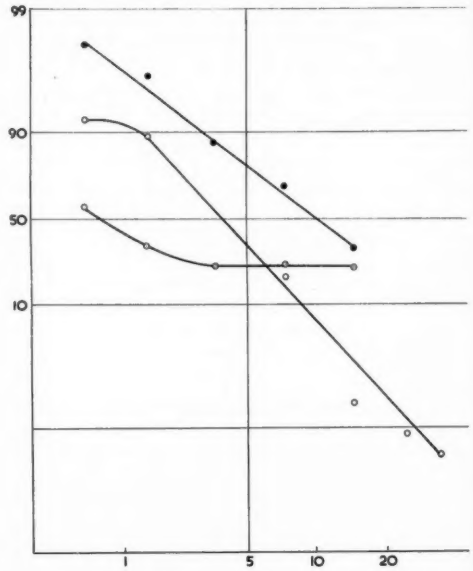


FIGURE XIII.
The age incidence of *H. influenzæ* meningitis and the case fatality according to age before the introduction of specific therapy in 1937 and between 1937 and 1948. Closed circles, case fatality before 1937. Circles with central dot, case fatality between 1937 and 1948. Open circles, age incidence of all cases on arbitrary logarithmic scale. Data from Dolphin and Popham (1951).

the influenza bacillus across the various boundaries intervening between throat and meninges. The second is probably immunological.

Incidentally, it is perhaps advisable to indicate the remarkable effect that treatment has had on case fatality, particularly in infants aged under two years. In working over vital statistics of the sort we are dealing with, one's major impression is the regularity of the findings. There is a statistical determinism about the onslaught of disease and death that is intimidating until one looks at a graph like Figure XIII, which shows clearly what effective therapeutic intervention can do.

At the laboratory level there have been a number of studies on the response of mice of various ages to virus infection, which have some relevance. Peripheral inoculation into suckling mice of an encephalitic virus like that of Murray Valley encephalitis will lead invariably to fatal encephalitis, but between the ages of two and four weeks this susceptibility rapidly diminishes. Four to six weeks old mice are fully susceptible to intracranial inoculation, but peripheral inoculation produces only a minimal viræmia and encephalitis does not occur. The failure of Coxsackie viruses to produce symptoms in mice more than a week old is another example.

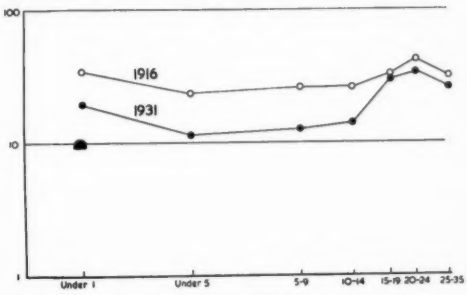


FIGURE XIV.
Case fatality rates by age for two New York City epidemics of poliomyelitis, 1916 and 1931. (International Committee, 1932.)

In general the changes in case fatality with age run parallel to the ratio of clinical to subclinical cases. Death is after all the climax of clinical manifestations. An interesting sidelight on this can be seen in Figure XIV, in which the case fatality rates by age are shown for the two big New York epidemics of poliomyelitis of 1916 and 1931. By 1931 many more non-paralytic cases were being diagnosed, cases which in 1916 were unrecognized and therefore in one sense subclinical. The apparent case fatality in children was much lower in 1931, but in adolescents and young adults, in whom a higher proportion of infections are frankly paralytic, the difference in case fatality between the two years is much less marked.

III. THE INFLUENCE OF IMMUNITY

The general effect of specific immunity on the incidence of overt disease has been demonstrated in the examples of measles, diphtheria and poliomyelitis. At each age the number of observed cases is determined by (i) the proportion of non-immune individuals, (ii) the intensity of exposure, and (iii) the ratio of clinical to subclinical infection. In any given year or series of years the absolute number of cases will be influenced by the virulence of the current strains of the responsible microorganism, but their distribution over the various ages is likely to be much the same. I have described how the Malta epidemic of poliomyelitis affected very heavily the same young age group which in the ten previous years had provided one or two cases per year. When diphtheria first appeared as an epidemic disease in its modern form in 1859, the incidence was on the youngest age group. In the years preceding the commonest clinical manifestation had been "croup" (laryngeal diphtheria), occurring only in an occasional infant. But the diphtheria bacillus had been sufficiently active subclinically to ensure immunization of substantial degree quite early in life. The important factor in determining the shape of the curve of incidence in the logarithmic form that we have used throughout is the intensity of exposure. This in its turn depends mainly on the degree of crowding and uncleanliness in the population on the one hand, and on specific qualities of the disease being considered on the other. If the pathogen in question is capable of infecting in minute doses, if it is liberated from the infected individual in large amount and for long periods, all these factors will increase the intensity of exposure.

Reasoning of this sort is applicable only to those infections which are followed either by permanent immunity or by sufficient immunity to ensure that with rare exceptions renewed infection is always subclinical and serves simply to reinforce immunity and maintain it at a roughly constant level. Where immunity is quite short-lasting, as in most of the common respiratory infections, no clear pattern of age incidence can be observed. What figures are available suggest that the incidence of influenza is much the same over different age groups. As I have already indicated, the incidence of fatality may have a very definite pattern indeed.

IV. MATERNALLY TRANSMITTED IMMUNITY

The part played by maternally transmitted passive immunity in infancy is doubtless important, particularly in heavily endemic areas: but it is equally true that an infant on the breast is automatically protected against a wide range of infection. Children under one year show a lower incidence for nearly all infections than children a year or two older; but it is hard to be sure whether this is mainly due to passive immunity or depends essentially on protection from contact with infection. It is interesting that the case fatality for

diphtheria and scarlet fever is recorded as lower than would be expected for infants under one year (see Figure III), and that it is very considerably lower for girl babies than for boys. I have wondered whether this might indicate that girls tend to retain their mothers' antibody in the circulation longer than boys.

It is possible that in one sense the most "physiological" time to have any type of infection is when maternal immunity has begun to fade, so that the infection is modified and produces only trivial symptoms, but is sufficiently definite to produce lasting active immunity. This is an idea I have borrowed from Dr. Joseph Stokes, junior, of Philadelphia, who has recently been extremely interested in the general possibilities of what he calls "passive-active" immunization. At what is at present a speculative level he has asked whether we should perhaps consider the possibility first of making certain that the mother has a normal immunity and then infecting the infant in its first few months of life with measles and mumps as well as immunizing it against diphtheria and pertussis. The possibility of including infection with the poliomyelitis viruses at the same time will almost certainly come up for discussion in the near future.

V. Allergic Aspects of Infection

It would be going outside the theme of this lecture to attempt to deal with a number of clinically important conditions, which are infections in the sense that pathogenic microorganisms are concerned, but which appear to depend essentially on special susceptibility in the patient, either inborn or acquired. Rheumatic fever is the most important, but others which may be mentioned are the high susceptibility of young women to tuberculosis, acute osteomyelitis in children, and acute nephritis. There are interesting problems in the age incidence of these conditions, but they are not directly relevant to the present discussion.

Conclusion

In working over material for this lecture I have been struck by the vivid contrast between the medical statistician's approach and that of the practising doctor. In the graphs that I have shown of case fatality by ages, every point is a distillation of the experience of hundreds of doctors tending thousands of sick children. A statistical regularity emerges from a collection of events, in every one of which the doctor has had to contend with all the individual circumstances of a sick child, his home environment, his inherited constitution and all the accidents that may swing the balance one way or another. This contrast between the unpredictability of the individual instance and the statistical regularity of occurrences in the aggregate permeates the whole of science. Even the behaviour of the ultimate particles of physics we are told is indeterminate as long as we consider them as individuals. In experimental biology we take it for granted that each living unit we have to deal with differs to some extent from every other similar unit, but that if we use enough of them we shall obtain quantitatively reproducible results. Perhaps that is why a red cell suspension is one of our most popular reagents—it is almost the only sort of preparation where similar biological units can be handled in millions.

In the graphs I have presented and discussed there are many variables hidden within their apparent orderliness. Probably the most important are concerned with the genetic constitution of the individuals who make up the populations concerned. I believe that we shall eventually find that this plays as important a part in many other infections as it is known to play in tuberculosis. We may find, for instance, that inheritance more than anything else determines which children will develop paralytic poliomyelitis instead of subclinical infection. Every biological happening, including an attack of disease or a death from infection, is determined in part by the inborn genetic equipment of the individual, in part by the past influence of his environment since birth, and in part by the activity of the immediate ætiological agent. I hope that this point of view has been implicit in all my discussion of the age distribution of infectious disease and death. Further advance in the control and treatment of infectious disease will probably call for more attention to the first two factors. We understand the pathogenic microorganism and the nature of its attack on the body rather well. We know very little indeed about genetic factors and the long-term influence of minor nutritional or psychological deviations from normality.

The regularity of the trends of curves of case fatality with age must represent in part a regularity in the distribution of certain genetically determined attributes through the community, just as it must equally involve a certain regularity of change with age in physiological adaptability. When we eventually reach a real understanding of what lies behind the superficial picture that I have presented, we may find that we have some hard thinking to do. It may be that we shall have to recognize that mortality in infancy and childhood in the past

has been the necessary price that had to be paid to prevent genetic deterioration, and that some of our modern successes in preventive and curative medicine may on the longest view be against the best interests of the race. But we have very far to go before we can justify any departure from the tradition of our profession that we should seek to provide for every individual the fullest measure of health and the longest enjoyment of life. Until human affections fade or human heredity becomes an open book we can do no other.

APPENDIX

I am greatly indebted to Dr. H. O. Lancaster, of the School of Public Health and Tropical Medicine, University of Sydney, for the information and calculations on which the following notes are based.

The regularity shown in the rise of mortality with age, for example in the case of respiratory infections, is to be regarded as an empirical relationship analogous to the Gompertz - Makeham law. In many of the infective diseases the logarithm of the mortality rate is, approximately, linearly related to the logarithm of the age.

The relationship between age and case fatality for various childhood diseases as shown in Figure III has as far as we are aware not been previously expressed in this form. The result shown graphically in the figures can also be expressed as follows:

> If y is the logarithm of the death rate per million *per annum* and x is the logarithm of the age in years, then x and y are related by the formula, $y=Ax+B$, which may be represented graphically by a straight line, the slope of which is A and B is the value of y corresponding to $x=0$, that is at one year exactly.

The equation may also be written: Death rate= (Age) $A \times 10^B$. In calculating this relationship, it has been assumed that the deaths under one year of age are centred round age 0·75 year and that at other ages deaths occur centred about the mid-year of the age. The constant A measures the fall of mortality with age, while B provides a measure of the intensity of the mortality. Table I shows values of A and B

TABLE I.

Period.	Mortality.	
	Intestinal Infections.	Respiratory Infections.
1908–1910	A −2·51 B 4·08	A −1·62 B 3·68
1911–1920	A −2·42 B 4·00	A −1·54 B 3·69
1921–1930	A −2·34 B 3·81	A −1·60 B 3·66
1931–1940	A −1·95 B 3·30	A −1·56 B 3·53
1941–1945	A −1·78 B 3·10	A −1·67 B 3·43

for the two "non-specific" groups of respiratory and bowel infections in Australia over the period covered by Lancaster's recent investigations on Australian mortality experience. The use of the two constants to provide a compact description of the changing experience of mortality in childhood may provide a valuable new approach to the understanding of the conditions involved.

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THE ACTION OF " REGITINE " IN MAN WITH SPECIAL REFERENCE TO ITS ADRENERGIC BLOCKING ACTION[1]

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INTRODUCTION

In clinical medicine, a reliable adrenergic blocking agent would be of great value in testing for a phæochromocytoma. This tumour produces a remediable hypertension through the production of norepinephrine and epinephrine. Adrenergic blocking agents previously used belong mainly to two groups—the benzodioxanes (of which " 933F " is the one commonly used) and " Dibenamine " and various closely related substances. Both these groups of drugs have serious disadvantages, as they may produce unpleasant reactions (Barnett, 1950, 1951) or give " false " results (Evans *et alii*, 1951; Mason, 1951). It was therefore important to determine whether the recently introduced " Regitine " (C7337) is more satisfactory for use in a test for circulating epinephrine and norepinephrine.

PHARMACOLOGICAL ACTION OF " REGITINE "

" Regitine ", 2-(N-p′-tolyl-N-(m′-Hydroxyphenyl)-Aminomethyl)-Imidazoline, or C7337, synthesized by Marxer and Hartman (see Trapold *et alii*, 1950), has the structural formula shown in Figure I.

In the experimental animal, the pharmacological action of this drug has been investigated by Meier *et alii* (1949), Longino *et alii* (1949), Trapold *et alii* (1950), and it has been found to be a potent, relatively non-toxic adrenergic blocking agent, and a less active sympatholytic agent.

It increases the survival rate against an otherwise fatal dose of epinephrine, and prevents the rise in blood pressure from epinephrine. It counteracts the effects of this substance on various smooth muscles—including the relaxing effect on the isolated rabbit ileum and the contracting effect on the non-gravid rabbit uterus and nictitating membrane of the cat. It does not, however, have any direct myotropic stimulating effect (Meier *et alii*, 1949). Its action against the metabolic effects of epinephrine apparently vary with the species. Thus Meier *et alii* (1949) stated that in rabbits epinephrine hyperglycæmia was not prevented, whereas Trapold *et alii* (1950) noted in dogs that the hyperglycæmic response to epinephrine was reduced and that the hypoglycæmia produced by insulin was prolonged. They stated that any severe toxic effects following " Regitine " administration were mainly due to hypoglycæmia.

In man, Longino *et alii* (1949) noted that, given intravenously (1·0 to 1·5 milligrammes per kilogram), " Regitine " produced a fall in blood pressure in hypertensive and most

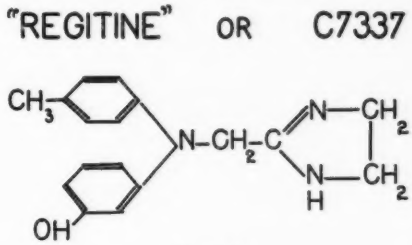

FIGURE I

normotensive persons. There was an increase in pulse rate and in temperature of the limbs. The drug was well tolerated orally (in doses varying from 25 milligrammes every four hours to 100 milligrammes every two hours). Freis *et alii* (1951), in observations on three subjects only, noted that, in an intravenous dose of 25 to 50 milligrammes, " Regitine " reversed the epinephrine pressor response, and exaggerated the epinephrine tachycardia, but only partially inhibited the pressor response to norepinephrine. These workers did not report separately on changes of the systolic and diastolic blood pressures, but only on the " mean arterial pressure ", which they took as the average of the systolic and diastolic blood pressures).

On account of its adrenergic blocking action, " Regitine " has been used as a test substance for the presence of a phæochromocytoma and in treatment of patients harbouring this

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tumour. Grimson *et alii* (1949) found that intravenous injection of "Regitine" (0·33 milligramme per kilogram) into a boy suffering from a phæochromocytoma (later proved by pathological examination) produced a fall in the arterial blood pressure from a markedly hypertensive to a normotensive level. Grimson (1950) has since used intravenous "Regitine" in two other patients with phæochromocytoma with a similar result. Emlet *et alii* (1951) stated that a single intramuscular injection of 5·0 milligrammes of "Regitine" produced a marked fall in the blood pressure of patients suffering from phæochromocytoma, but only a slight fall in patients with essential hypertension. On the other hand, Gifford *et alii* (1951) found that 5·0 milligrammes of "Regitine" given by intramuscular injection produced a definite fall in blood pressure in only one of three patients with persistent hypertension from a phæochromocytoma; in the other two, subsequent intravenous injection of 5·0 milligrammes produced a fall. Iseri *et alii* (1951) successfully treated a patient with sustained hypertension from a phæochromocytoma with orally administered "Regitine", in doses of 25·0 milligrammes every three hours for a period of 29 days.

No serious toxic effects have been reported from the administration of "Regitine" to humans. Longino *et alii* (1949) reported that three patients receiving respectively 1·0, 1·2 and 1·5 milligrammes per kilogram intravenously experienced substernal pain.

OBSERVATIONS

Method

All investigations were carried out with the subjects lying comfortably in a quiet room. Infusions of l-epinephrine hydrochloride or of l-norepinephrine bitartrate monohydrate and injections of "Regitine" were given into separate veins in the same arm. The blood pressures were recorded from the other arm by sphygmomanometry. The epinephrine and norepinephrine solutions were diluted in a 5% glucose solution so that each millilitre contained 5·0 microgrammes of the active substance expressed in terms of the base. The infusion was given through a two-way tap and plastic adapter connected to a needle. Before and after the administration of the epinephrine and norepinephrine, 5% glucose solution was given by the other arm of the two-way tap. Intravenous injections of "Regitine" were given over a period of five minutes, and were preceded and followed by an injection of normal saline, so as to obviate any disturbance from the venepuncture, or from knowledge by the subject of the precise time of administration of the active agent. The findings in one subject are shown in detail in Figure II and the results of the various investigations are summarized in subsequent figures.

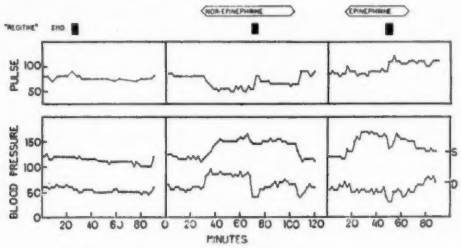

FIGURE II

Chart showing the effect in a normotensive subject of an intravenous injection of "Regitine" given (*a*) alone, (*b*) during an intravenous infusion of norepinephrine, and (*c*) during an intravenous infusion of epinephrine. S = systolic; D = diastolic

Findings

For descriptive purposes a change in the blood pressure (millimetres of mercury) or pulse rate (beats per minute) of 0 to 9 will be called "insignificant", 10 to 19 "slight", 20 to 29 "moderate" and 30 and over "marked".

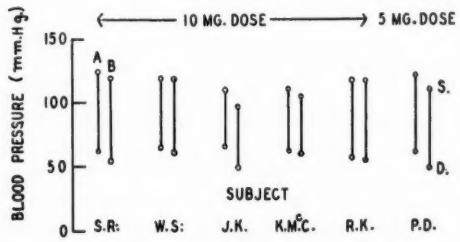

FIGURE III

Intravenously administered "Regitine" in normotensive persons. A = blood pressure before "Regitine"; B = blood pressure after "Regitine". S = systolic; D = diastolic

1. *The Effect of Intravenously Injected "Regitine" in Normotensive Persons* (*Table I and Figure III*).—"Regitine", 10·0 milligrammes, was given intravenously to five normal persons, and 5·0 milligrammes to another person. There resulted no change or an insignificant fall in the systolic and diastolic blood pressures in four, and a slight fall in these pressures in two subjects. There was no change or an insignificant rise in the pulse rate in three, and a slight rise in the other three subjects.

2. *The Effect of Intravenously Administered "Regitine" in Subjects Receiving an Intravenous Infusion of l-norepinephrine* (*Table II and*

TABLE I

The Effect of an Intravenous Injection of "Regitine" in Normotensive Persons

Subject.	Age.	Sex.	Weight. (Kilo-grams.)	"Regitine" Dose. (Milli-grammes.)	Base-line * Blood Pressure. (Millimetres of Mercury.)		Lowest Blood Pressure Readings Following "Regitine". (Millimetres of Mercury.)		Change in Blood Pressure After "Regitine". (Millimetres of Mercury.)		Base-line Pulse Rate (per Minute).	Highest Pulse Rate After "Regitine" (per Minute).	Changes in Pulse Rate After "Regitine" (per Minute).
					Sys-tolic.	Dias-tolic.	Sys-tolic.	Dias-tolic.	Sys-tolic.	Dias-tolic.			
S.R.	24	M.	72	10	124 (122–126)	62 (58–66)	118	54	−6	−8	69 (68–70)	84	+15
W.S.	28	M.	76	10	118 (114–120)	64 (62–66)	118	60	0	−4	62 (60–70)	76	+14
J.K.	23	M.	74·5	10	109 (104–110)	65 (64–66)	96	48	−13	−17	70 (66–72)	78	+8
K.McC.	26	M.	70	10	110 (108–112)	62 (60–66)	104	58	−6	−4	62 (58–64)	66	+4
P.D.	24	M.	62	5	120 (118–122)	62 (58–64)	108	48	−12	−14	80 (78–82)	92	+12
R.K.	31	M.	70	10	116 (112–122)	56 (52–58)	116	54	0	−2	89 (86–94)	94	+5

* Base-line figures are obtained from an average of determinations over a period of approximately 10 minutes prior to the injection of "Regitine".

Figure IV).—During the course of an intravenous infusion of l-norepinephrine (0·18 to 0·27 microgramme per kilogram per minute), five subjects received an intravenous injection of 10·0 milligrammes of "Regitine". This was followed by a fall in the systolic and

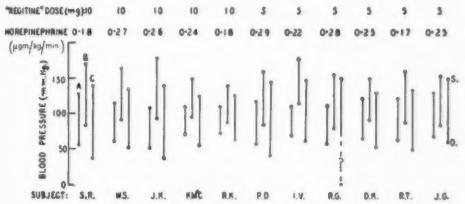

FIGURE IV

Intravenously administered "Regitine" in persons receiving intravenous injections of norepinephrine. A = base-line blood pressure; B = blood pressure during norepinephrine infusion; C = blood pressure during norepinephrine infusion *plus* injection of "Regitine". S = systolic; D = diastolic

diastolic blood pressures in all subjects. The fall in the systolic blood pressure was slight in one instance, moderate in three and marked in one instance. The fall in the diastolic blood pressure was moderate in one and marked in the other four. In all five subjects this pressure fell to a value lower than the pre-norepinephrine base-line level. The pulse rate rose in all five instances, the rise being moderate in four and marked in one. In all subjects the rise was to a level above the pre-norepinephrine base-line value.

During the course of an intravenous infusion of l-norepinephrine (0·17 to 0·29 microgramme per kilogram per minute), six subjects received an intravenous injection of 5·0 milligrammes of "Regitine". In two of these the change in the systolic blood pressure was insignificant; in the other four there was a definite fall (slight in one, moderate in three). In all six there was a fall in the diastolic blood pressure (moderate in one and marked in five) to a level lower than the pre-norepinephrine base-line value. The pulse rate showed an insignificant change in two subjects, and a moderate rise in the other four. In only one instance did the pulse rate rise significantly above the pre-norepinephrine base-line value.

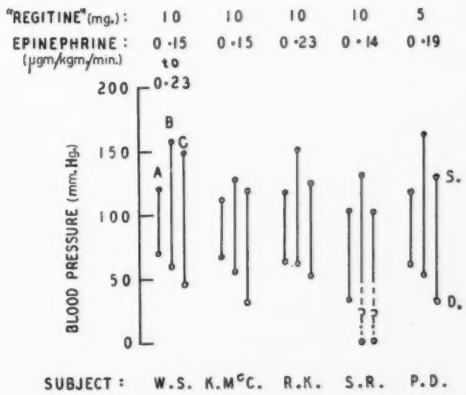

FIGURE V

Intravenously administered "Regitine" in persons receiving intravenous injections of epinephrine. A = base-line blood pressure; B = blood pressure during epinephrine infusion; C = blood pressure during epinephrine infusion *plus* "Regitine". S = systolic; D = diastolic.

3. *The Effect of Intravenously Administered "Regitine" in Subjects Receiving an Intravenous Infusion of l-epinephrine* (*Table III and Figure V*).—During the course of a continuous

TABLE II.

The Effect of an Intravenous Injection of "Regitine" in Normotensive Persons Receiving a Continuous Infusion of l-Norepinephrine.

Subject.	Age.	Sex.	Weight. (Kilograms.)	"Regitine" Dose. (Milligr'm's.)	Norepinephrine Dose. (Micrograms per Kilogram per Minute.)	Intravenous Glucose Base-line Blood Pressure. (Millimetres of Mercury.)		Norepinephrine Base-line Blood Pressure. (Millimetres of Mercury.)		Lowest Blood Pressure after "Regitine". (Millimetres of Mercury.)		Change in Blood Pressure after "Regitine". (Millimetres of Mercury.)		Intravenous Glucose Base-line Pulse Rate (per Minute).	Norepinephrine Base-line Pulse Rate (per Minute).	Highest Pulse Rate after "Regitine" (per Minute).	Change in Pulse Rate after "Regitine" (per Minute).
						Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.				
S.R.	24	M.	72	10	0·18	126 (124–126)	55 (52–60)	168 (160–180)	82 (78–90)	138	36	−30	−46	83 (80–88)	70 (62–76)	102	+32
W.S.	28	M.	76	10	0·27	114 (112–116)	60 (56–64)	163 (156–168)	90 (82–94)	134	50	−29	−40	62 (58–66)	56 (52–60)	80	+24
J.K.	23	M.	74·5	10	0·26	107 (104–110)	50 (48–52)	176 (164–186)	91 (78–96)	138	36	−38	−58	60 (60–62)	53 (50–54)	74	+21
K.McC.	26	M.	70	10	0·24	108 (104–112)	70 (66–74)	148 (144–152)	94 (90–96)	124	54	−24	−40	55 (54–56)	44 (44–46)	64	+20
R.K.	31	M.	70	10	0·18	109 (108–112)	71 (68–74)	138 (136–144)	86 (80–90)	120	62	−18	−24	76 (70–80)	60 (58–64)	86	+26
P.D.	24	M.	62	·5	0·29	116 (112–120)	56 (54–58)	158 (152–164)	84 (80–88)	144	40	−18	−44	81 (78–82)	55 (52–60)	80	+25
I.V.	23	M.	70	5	0·22	109 (108–112)	68 (64–74)	175 (172–176)	114 (110–118)	146	60	−29	−54	63 (62–64)	61 (60–62)	62	+1
R.C.	26	M.	74·5	5	0·28	110 (108–112)	56 (54–60)	154 (150–160)	78 (76–82)	148	(?) 0*	−6	(?) −78*	62 (58–68)	46	74	+28
D.K.	22	M.	70·5	5	0·25	120 (118–128)	64 (62–68)	148 (144–152)	90 (88–92)	128	52	−20	−38	74	56 (54–56)	78	+22
R.T.	20	M.	87·2	5	0·17	120 (118–126)	61 (58–64)	158 (150–168)	86 (80–96)	132	48	−26	−38	54 (52–56)	44 (42–48)	52	+8
J.G.	23	M.	74·5	5	0·25	129 (126–132)	66 (64–68)	152 (148–156)	83 (80–86)	148	60	−4	−23	80 (76–86)	57 (54–62)	80	+23

* In this instance no diastolic end point could be determined at one stage following the injection of "Regitine". Base-line figures are obtained from an average of determinations over a period of approximately 10 minutes prior to change of infusion (intravenously injected glucose base-line) or injection of "Regitine" (norepinephrine base-line). Figures in brackets denote the highest and lowest readings over the base-line period.

TABLE III.

The Effect of an Intravenous Injection of "Regitine" in Normotensive Persons Receiving a Continuous Infusion of l-Epinephrine.

Subject.	Age.	Sex.	Weight. (Kilograms.)	"Regitine" Dose. (Milligr'm's.)	Epinephrine Dose. (Micrograms per Kilogram per Minute.)	Intravenous Glucose Base-line Blood Pressure. (Millimetres of Mercury.)		Epinephrine Base-line Blood Pressure. (Millimetres of Mercury.)		Lowest Blood Pressure after "Regitine". (Millimetres of Mercury.)		Change in Blood Pressure after "Regitine". (Millimetres of Mercury.)		Intravenous Glucose Base-line Pulse Rate (per Minute).	Epinephrine Base-line Pulse Rate (per Minute).	Highest Pulse Rate after "Regitine" (per Minute).	Change in Pulse Rate after "Regitine" (per Minute).
						Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.				
S.R.	24	M.	72	10	0·14	101 (100–104)	34 (32–38)	130 (122–134)	0 (?)	100	0(?)	−30	—	70 (68–72)	108 (104–112)	126	+18
W.S.	28	M.	76	10	0·15 to 0·23	120 (116–128)	69 (66–72)	157 (146–164)	60 (54–66)	148	46	−9	−14	65 (60–68)	87 (84–90)	112	+25
K.McC.	26	M.	70	10	0·15	110 (104–116)	68 (60–74)	127 (124–130)	55 (50–58)	118	30	−9	−28	46 (44–48)	61 (58–64)	78	+17
P.D.	24	M.	62	5	0·19	118 (116–120)	60 (52–70)	163 (158–166)	52 (46–60)	134	30	−29	−22	84 (82–84)	91 (90–92)	120	+29
R.K.	31	M.	70	10	0·23	117 (116–118)	63 (60–68)	150 (144–160)	62 (60–64)	124	50	−26	−12	75 (74–76)	102 (100–104)	124	+22

intravenous infusion of l-epinephrine (0·14 to 0·23 microgramme per kilogram per minute), an intravenous injection of 10·0 milligrammes of "Regitine" was given to four subjects and 5·0 milligrammes to another. Following the injection of "Regitine" there was an insignificant fall in the systolic blood pressure in two subjects and a moderate fall in the other three. (However, in one subject, W.S., in whom the fall was recorded as "insignificant", the epinephrine infusion did not have the desired constancy and the systolic blood pressure was rising when the intravenous injection of "Regitine" was given; the rise gave way to a slight fall. In the other subject, K.McC., in whom the fall in systolic blood pressure is recorded as "insignificant", the rise in this pressure produced by the epinephrine infusion was only slight, and thus no marked fall could be expected.) In the four subjects in whom the observation could be made there was a fall in the diastolic blood pressure, this being slight in two cases and moderate in the other two. (In one subject it was not possible to observe the effect of the intravenous injection of "Regitine" on the diastolic blood pressure, as no diastolic end-point was obtainable during the epinephrine infusion.) In all five subjects the pulse rate, which had already risen under the influence of the epinephrine infusion, showed a further rise following the injection of "Regitine".

4. *The Effect of Intramuscularly Administered "Regitine" in Subjects Receiving an Intravenous Infusion of l-norepinephrine.*—Two subjects received an intramuscular injection of 10·0 milligrammes of "Regitine" during the course of an intravenous infusion of l-norepinephrine (0·13 and 0·17 microgramme per kilogram per minute). In the first subject a definite, but delayed, fall in the systolic and diastolic blood pressures followed the "Regitine" injection. In the second subject (Figure VI), following the "Regitine" injection, there was a slight fall only in the diastolic blood pressure and no significant change in the systolic pressure. However, following a subsequent intravenous injection of 10·0 milligrammes of "Regitine" there was a marked fall in the diastolic blood pressure and a slight fall in the systolic pressure.

5. *The Effect of Orally Administered "Regitine" on the Response to a Subsequent Intravenous Infusion of l-norepinephrine.*—One subject took 40·0 milligrammes of "Regitine" orally one and a half hours before receiving an intravenous infusion of l-norepinephrine (0·23 microgramme per kilogram per minute). The pressor response was not prevented. On a subsequent day he took 100 milligrammes of "Regitine" orally two hours before receiving a norepinephrine infusion (0·18 microgramme per kilogram per minute). The pressor response was not significantly less than the response without a prior dose of "Regitine". (The experimental conditions in this case were not ideal. The subject took the "Regitine" tablets at home before breakfast and then travelled to the hospital for the test).

Two other subjects, after an infusion of norepinephrine (0·17 and 0·18 microgramme per kilogram per minute) to determine their response when not influenced by another drug,

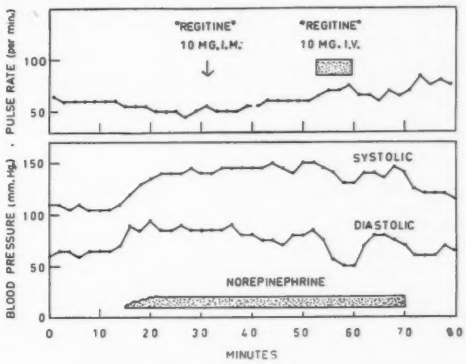

FIGURE VI

Effect of intramuscular and intravenous injection of "Regitine" in a subject receiving an intravenous infusion of l-norepinephrine.

were given 100 milligrammes of "Regitine" in water orally under supervision. Following this, repeated infusions of l-norepinephrine in similar dosage to that employed previously were given at intervals over two hours. In both subjects the rise in diastolic blood pressure from norepinephrine was prevented (in one instance being replaced by a slight fall). The effect on the rise in systolic blood pressure was less marked (Figure VII). In one subject the norepinephrine blocking effect was still markedly present two hours after the injection of "Regitine"; in the other it had decreased.

6. *The Effect of Intravenously Administered "Regitine" in Hypertensive Persons (Table IV and Figure VIII).*—Eight hypertensive subjects received an intravenous injection of 10·0 milligrammes of "Regitine". In one patient (K.K.) this was followed by a rise in the systolic blood pressure. In the other seven there was a fall in the systolic blood pressure (slight in three, moderate or marked in four). In one patient (D.D.) there was no significant change in the diastolic blood pressure; in the other seven there was a fall in this pressure (slight

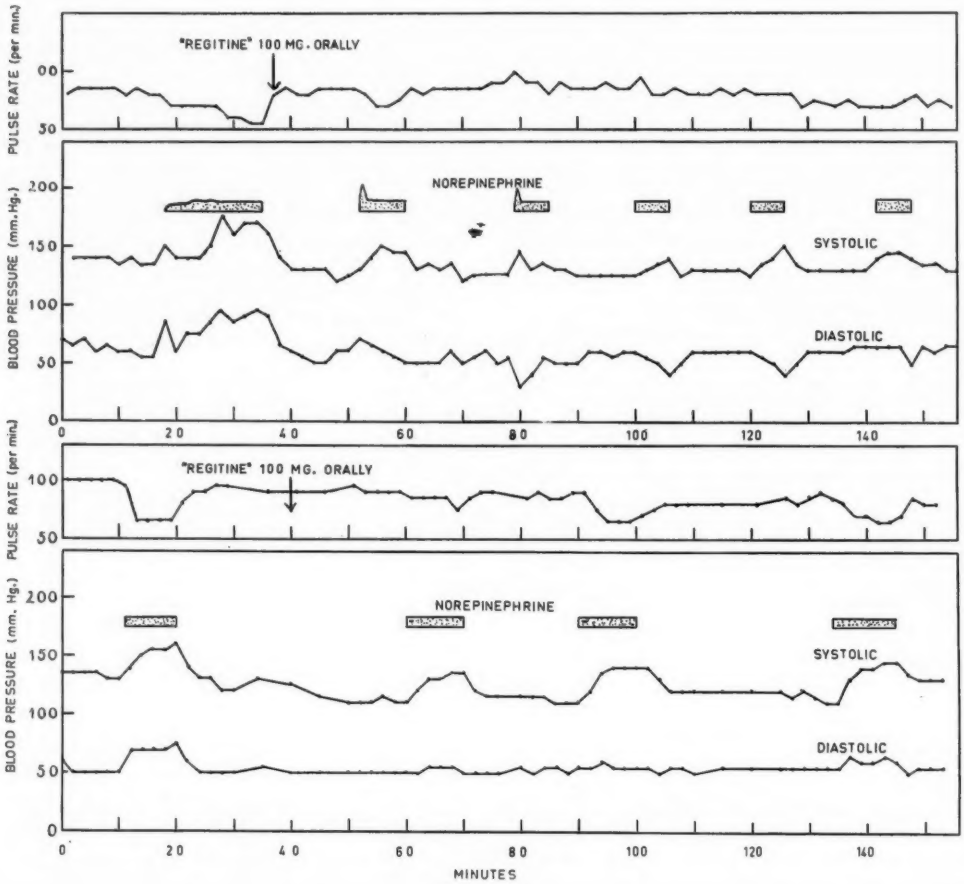

FIGURE VII

The effect on the response to an intravenous infusion of l-norepinephrine produced by an oral dose of 100 milligrammes of " Regitine "

in three, moderate or marked in four). In only one patient (A.K.) did the diastolic blood pressure fall to a normotensive level (less than 90 millimetres of mercury). This man had a large left-sided suprarenal tumour which, after operation, was proved to be a cortical neoplasm. His arterial hypertension (which was only slight) returned during convalescence.

Four hypertensive subjects received an intravenous injection of 5·0 milligrammes of " Regitine ". In all four there was a marked or moderate fall in the systolic blood pressure and a slight fall in the diastolic pressure. In no instance did the blood pressures fall to a normotensive level (150 millimetres of mercury systolic, 90 millimetres diastolic).

In 11 patients the fall in blood pressure from the intravenous injection of 10·0 or 5·0 milligrammes of " Regitine " was compared with that produced by the intramuscular injection of 2·0 milligrammes of hexamethonium

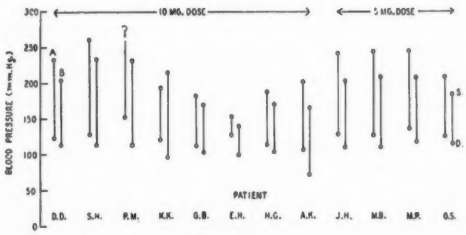

FIGURE VIII

Intravenously administered " Regitine " in hypertensive persons. A = blood pressure before " Regitine "; B = blood pressure after " Regitine ". S = systolic; D = diastolic

bromide (Table V). In all instances the fall in systolic blood pressure produced by the

TABLE IV.

The Effect of an Intravenous Injection of "Regitine" in Hypertensive Persons.

Subject.	Age.	Sex.	Weight. (Kilo-grams.)	Clinical Diagnosis.	"Regitine" Dose. (Milli-grammes.)	Base-line Blood Pressure. (Millimetres of Mercury.)		Lowest or Highest Blood Pressure after "Regitine". (Millimetres of Mercury.)		Change in Blood Pressure after "Regitine". (Millimetres of Mercury.)		Base-line Pulse Rate. (per Minute).	Highest or Lowest Blood Pressure after "Regitine" (per Minute).	Change in Pulse Rate after "Regitine" (per Minute).
						Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.			
D.D.	27	F.	53	Chronic nephritis.	10	231 (224–249)	123 (116–128)	204	114	−27	−7	98 (96–100)	120	+22
S.H.	52	F.	41	Essential hypertension, malignant phase.	10	260 (254–260)	129 (126–134)	234	114	−26	−15	113 (104–116)	96	−17
P.M.	46	F.	38	Essential hypertension, malignant phase.	10	260+	152 (150–154)	232	114	−28+	−38	120 (116–126)	148	+28
K.K.	41	F.	60	Essential hypertension, benign phase.	10	194 (192–196)	122 (116–126)	216	96	+22	−26	85 (80–92)	121	+36
G.B.	49	M.	83	Essential hypertension, benign phase.	10	183 (176–190)	114 (112–114)	170	104	−13	−10	70 (68–70)	80	+10
E.H.	31	M.	62	Essential hypertension, benign phase.	10	154 (150–156)	134 (130–138)	140	100	−14	−34	107 (106–110)	120	+13
H.C.	49	M.	83·6	Essential hypertension, benign phase.	10	188 (176–200)	115 (112–120)	170	104	−18	−11	68 (66–70)	80	+12
A.K.	61	M.	70	Essential hypertension, benign phase.	10	202 (196–208)	108 (106–110)	166	72	−36	−36	67 (64–68)	84	+17
J.H.	53	M.	54	Essential hypertension, malignant phase.	5	242 (232–248)	130 (128–138)	204	112	−38	−18	73 (72–74)	76	+3
M.B.	51	F.	65	Essential hypertension, benign phase.	5	244 (234–252)	128 (124–132)	208	112	−36	−16	85 (84–86)	112	+27
M.P.	59	F.	40	Essential hypertension, malignant phase.	5	245 (242–248)	136 (134–138)	208	118	−37	−18	75 (74–76)	94	+19
C.S.	39	M.	55	Chronic pyelonephritis.	5	208 (204–214)	126 (124–128)	184	116	−24	−10	74 (72–76)	84	+10

TABLE V.

Comparison of Effects of an Intravenous Injection of "Regitine" and Intramuscular Injection of Hexamethonium Bromide (H.M.B.) in Hypertensive Persons.

Subject.	Age.	Sex.	Weight. (Kilograms.)	"Regitine" Dose. (Milligrammes.)	Effect of Intravenous "Regitine".						Effect of Intramuscular Hexamethonium Bromide. (H.M.B.)						
					Base-line Blood Pressure. (Millimetres Mercury.)		Lowest Blood Pressure after "Regitine". (Millimetres of Mercury.)		Fall in Blood Pressure after "Regitine". (Millimetres of Mercury.)		H.M.B. Dose. (Milligrammes per Kilogram.)	Base-line Blood Pressure. (Millimetres of Mercury.)		Blood Pressure Floor after H.M.B. (Millimetres of Mercury.)		Fall in Blood Pressure. after H.M.B. (Millimetres of Mercury.)	
					Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.		Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.
D.D.	27	F.	53	10	231 (224–244)	123 (116–128)	204	114	—27	—7	2	225	130	180	120	—45	—10
G.B.	48	F.	52	10	225 (220–230)	137 (136–140)	194	100	—31	—37	2	225	150	145	95	—80	—55
S.H.	52	F.	41	10	260 (254–260+)	129 (126–134)	234	114	—26	—15	2	235	125	190	115	—45	—10
P.M.	46	F.	38	10	260+	152 (150–154)	232	114	—38+	—38	2	250	140	130	85	—120	—55
K.K.	41	F.	60	10	194 (192–196)	122 (116–126)	216	96	+22	—26	2	160	100	150	100	—10	0
H.C.	49	M.	83	10	183 (175–190)	114 (112–114)	170	104	—13	—10	2	200	120	170	115	—30	—5
E.H.	31	M.	62	10	154 (150–156)	134 (130–138)	140	100	—14	—34	2	150	130	100	80	—50	—50
J.H.	53	M.	54	5	242 (232–248)	130 (128–138)	204	112	—38	—18	2	225	130	165	110	—95	—20
M.B.	51	F.	65	5	244 (234–252)	128 (124–132)	208	112	—36	—16	2	220	120	145	100	—75	—20
M.P.	59	F.	40	5	245 (242–248)	136 (134–138)	208	118	—37	—18	2	245	135	180	100	—65	—35
C.S.	39	M.	55	5	208 (204–214)	126 (124–128)	184	116	—24	—10	2	200	120	160	110	—40	—10

injection of the methonium compound was greater than that following the injection of the " Regitine ". The fall in the diastolic blood pressure produced by the methonium and " Regitine " was similar (less than 10·0 millimetres difference in the falls) in six subjects, the fall produced by the methonium compound was the greater in four, and in one subject (K.K.) the fall after the " Regitine " administration was the greater. However, in this patient the base-line blood pressures were widely different at the times of the two investigations.

General Remarks

The effects of " Regitine " given intravenously became apparent during the actual injection and lasted only some fifteen minutes.

With the possible exception to be mentioned, no toxic effects worthy of comment have occurred from " Regitine " in the dose used. One subject receiving 100 milligrammes of " Regitine " orally, although experiencing no toxic symptoms while the investigation was being carried out, vomited on return to his own ward. However, he had a surgical condition which might in itself have caused vomiting.

DISCUSSION

These observations have demonstrated that, in man, " Regitine " has a blocking action against certain of the effects of epinephrine and norepinephrine. Thus it usually decreases the rise in systolic blood pressure produced by epinephrine. However, it does not prevent the fall in diastolic blood pressure from epinephrine, which is in fact exaggerated. This would suggest that, while diminishing certain excitory effects of epinephrine, it does not block certain inhibitory effects. Also it does not prevent epinephrine-induced tachycardia, but rather augments it. In the case of norepinephrine, " Regitine " diminishes the pressor response, the effect being much more marked on the diastolic than on the systolic pressure. In fact, after an injection of " Regitine " the diastolic blood pressure falls below the base-line value, and a diastolic end-point may be difficult to determine. The bradycardia due to norepinephrine is abolished. In persons receiving 5·0 milligrammes of " Regitine " the pulse rate usually returns to approximately its pre-norepinephrine base-line ; in persons receiving 10·0 milligrammes of " Regitine " it rises above this value. There is a general resemblance to the modification of the circulatory effects of epinephrine and norepinephrine by " Dibenamine " (Barnett, 1951). Important differences are the greater rapidity of onset and shorter duration of the effects of " Regitine " and the absence of any significant toxic effects. When " Regitine " was given intravenously during a norepinephrine infusion, the diastolic blood pressure fell below the base-line value. When " Dibenamine " was given during such an infusion, the fall was merely towards the base-line.

The observation that an injection of 10·0 milligrammes of " Regitine " produces but a slight fall in the blood pressure in normotensive persons, whereas this dose completely blocks the rise of diastolic blood pressure from intravenous norepinephrine, indicates that the normal blood pressure depends little, if at all, on circulating norepinephrine.

Again, the observation that the injection of 5·0 milligrammes of " Regitine " produces only a slight fall in the blood pressure of hypertensive subjects, but blocks the diastolic rise from intravenously administered norepinephrine, indicates that the raised diastolic blood pressure in the hypertensives depends little, if at all, on an increased amount of circulating norepinephrine. This conclusion was previously reached from other evidence (Barnett *et alii*, 1950).

The results of animal investigations (Meier *et alii*, 1949) indicate that a smaller dose of " Regitine " is required for an " adrenolytic " than for a " sympatholytic " effect. The observations reported above would indicate that this is not due to greater facility in blocking the effects of epinephrine than of norepinephrine. Presumably it is easier to block the effect of circulating norepinephrine than of norepinephrine liberated in close proximity to cells. The observation that when the base-line blood pressures are similar the intravenous injection of 10·0 milligrammes of " Regitine " produces less fall in blood pressure in some hypertensive persons than the intramuscular injection of hexamethonium bromide (2·0 milligrammes per kilogram) suggests that the dose of " Regitine " used was not sufficient for complete sympathetic blockade. A comparison of the blood pressure fall produced by 10·0 milligrammes of " Regitine " in hypertensive and normotensive persons cannot be used as evidence concerning a possible sympathetic nervous component in human hypertension.

Various investigators have reported favourably on the use of " Regitine " as a test agent for the presence of a phæochromocytoma. The observations reported above indicate that " Regitine " is more effective in blocking the effects of norepinephrine than of epinephrine

and that the effect is more marked on the diastolic than on the systolic blood pressure. As most phæochromocytomata have been shown to contain mainly norepinephrine (West *et alii*, 1951) and as this produces a diastolic hypertension (Barnett *et alii*, 1950) these properties do not detract from the value of "Regitine" in such a test. The observation that in one subject an intramuscular injection of 10·0 milligrammes of "Regitine" had little blocking effect against the rise in blood pressure produced by norepinephrine, but that a subsequent intravenous injection of the same dose was followed by a prompt fall in blood pressure, suggests that the intravenous is preferable to the intramuscular route in the use of this drug in a test for circulating norepinephrine. Gifford *et alii* (1951) found that in two patients with phæochromocytoma the intramuscular injection of 5·0 milligrammes of "Regitine" was ineffective in producing a fall in blood pressure, whereas a subsequent intravenous injection of the same dose of the drug produced a fall. Our observation that the intravenous injection of 10·0 milligrammes of "Regitine" caused the diastolic blood pressure to fall to a normal level in one person with essential hypertension suggests that this dose may be too large as a test and that a dose of 5·0 milligrammes may be preferable. Past experience with adrenergic blocking agents warns us that it is unwise to put complete trust in their use in the diagnosis of the presence of a phæochromocytoma. Gifford *et alii* (1951) observed a marked fall in blood pressure following the injection of 5·0 milligrammes of "Regitine" in two of 179 patients with arterial hypertension without the presence of phæochromocytoma. One of these patients was in uræmia and the other heavily sedated. A definitely greater fall in the diastolic blood pressure after the intravenous injection of "Regitine" (5·0 milligrammes) than following the intramuscular injection of hexamethonium bromide (2·0 milligrammes per kilogram) would suggest the presence of a phæochromocytoma.

SUMMARY AND CONCLUSIONS

1. In normotensive persons, the intravenous injection of 5·0 or 10·0 milligrammes of "Regitine" produced a slight or negligible fall in the systolic and diastolic blood pressures.

2. In subjects with systolic and diastolic hypertension artificially produced by an infusion of l-norepinephrine, an intravenous injection of 5·0 or 10·0 milligrammes of "Regitine" partially blocked the rise in systolic, and completely blocked the rise in diastolic, blood pressure.

3. In subjects with systolic hypertension artificially produced by an infusion of l-epinephrine, an intravenous injection of 5·0 or 10·0 milligrammes of "Regitine" partially blocked the systolic rise in most instances. The diastolic blood pressure, which had usually decreased during the epinephrine infusion, fell further as a result of the "Regitine" injection.

4. In one subject, an intramuscular injection of 10·0 milligrammes of "Regitine" was ineffective in blocking the pressor response to norepinephrine, whereas a subsequent intravenous injection was effective.

5. In two of three subjects, orally administered "Regitine", 100 milligrammes, was effective in blocking the diastolic pressor response to norepinephrine.

6. In hypertensive persons, the intravenous injection of 5·0 or 10·0 milligrammes of "Regitine" was usually followed by some fall in blood pressure. In one person not harbouring a phæochromocytoma, after the intravenous injection of 10·0 milligrammes of "Regitine" the diastolic blood pressure fell to a normotensive level.

7. In the doses used, "Regitine" produced no toxic reactions.

8. These findings are discussed, and it is concluded that: (*a*) The evidence confirms the belief that neither normal blood pressure nor the raised blood pressure of essential hypertension is maintained by circulating norepinephrine. (*b*) The intravenous injection of 5·0 milligrammes of "Regitine" should be a valuable test for the diagnosis of a phæochromocytoma, but should be interpreted with care.

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DIABETES MELLITUS IN ASSOCIATION WITH LOWERED RENAL THRESHOLD TO GLUCOSE[1]

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THE occurrence of glycosuria without an elevation of the blood sugar content above the limits of normality has been recognized for many years. It is regarded by most physicians as of no clinical significance, its chief interest being that of differential diagnosis from the glycosuria associated with the hyperglycæmia of *diabetes mellitus*. The term lowered renal threshold to glucose, which is applied to this condition, implies that the kidneys permit the excretion of glucose, although the blood sugar content remains within normal limits. As far as is known the condition is benign; it shows some hereditary tendency (Hjarne, 1927), but it is not to be regarded as a precursor of *diabetes mellitus*. When once established, it apparently persists throughout life, and unless of extreme degree, produces no symptoms and requires no treatment. Much speculation has developed as to the reason for this aberrance of renal activity without any real solution of the problem being found. To those accustomed to the management of *diabetes mellitus* the condition has a peculiar interest, more particularly if it occurs in association with diabetes. It is customary in most instances, when attempting the control of diabetic patients, to rely on urine testing as a guide to the efficacy of treatment. However, should a diabetic patient have a lowered renal threshold to glucose it is apparent that, unless this abnormality is recognized, any attempt made to render the urine free of sugar may be accompanied by unpleasant and even disastrous consequences.

Possibly the earliest case of lowered renal threshold to be described was that of a patient of Klemperer (1896), whose urine contained 0·35% glucose while the level of the blood sugar was 0·18%. A few years later two eminent Continental authorities, Naunyn (1906) and von Noorden (1912) disagreed about its existence as a clinical entity. In 1913 F. M. Allen, after a review of the literature, applied the term "Clinical Renal Glycosuria" to embrace cases of "glycosuria with normal glycæmia relatively independent of diet". He stated: "The excretion of sugar must be due to abnormal permeability of the kidney, while the tissues still retain the normal power of utilizing dextrose." Following upon Cushny's theory of renal function, further knowledge has modified Allen's concept of abnormal permeability (Mirsky and Nelson, 1943). It is now known that the crystalloids of the blood are filtered through the glomeruli into the kidney tubules where they are either reabsorbed into the blood stream or concentrated and then excreted into the urine. The excretion of glucose must therefore depend on several factors—firstly its concentration in the arterial supply to the glomeruli, secondly the rate at which the glomeruli filter it out of the blood, and finally the rate at which it is reabsorbed by the tubules.

When the renal threshold is lowered in an otherwise normal individual the concentration of dextrose in the blood is not excessive and the glomerular filtration rate is not disturbed (Friedman *et alii*, 1942). The fault lies with the tubules whose ability to reabsorb glucose is so impaired as to allow glycosuria to occur at normal blood sugar concentrations. Some evidence exists to suggest that this is related to a disturbance of phosphatase activity (Marsh and Drabkin, 1947). Curiously enough at high plasma glucose levels (above 200 milligrammes per 100 cubic centimetres) the efficiency of tubular reabsorption has been found equal to or even higher than that of normal individuals (Nielson, 1948). Although no studies have been made upon this problem in any appreciable series of diabetic patients, it may be assumed that while tubular reabsorption proceeds at a normal rate during hyperglycæmia, the inherent defect permits glycosuria to occur when the blood sugar content has been reduced to normal limits. It is possible that other factors, as yet unknown, exert an influence on the rate of tubular reabsorption (Ekehorn, 1946). Doubtless these will eventually explain such phenomena as the transient lowering of the threshold which is occasionally observed during pregnancy. However, in most instances

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impaired tubular reabsorption, when once developed, persists throughout life.

From the standpoint of the clinician it would seem that the diagnosis of a lowered renal threshold to glucose would present little difficulty and in fact would conform to Allen's criteria of glycosuria with normal glycæmia. Thus it would include instances of intermittent glycosuria with normal glycæmia, if the threshold were not unduly lowered. Unfortunately, while most British and Continental authorities agree with this view, Joslin and his school (Marble *et alii*, 1939) demand that glycosuria be constant before the diagnosis is made. In other words the threshold must be lowered to a level which is impossible to determine. In consequence wide variation exists in reports of the incidence of renal glycosuria (Bland, 1948). Joslin and his associates reported 53 cases of renal glycosuria in 18,000 subjects showing glycosuria. Lyall (1946), on the other hand, found 234 cases of renal glycosuria in 387 soldiers with glycosuria on enlistment and Peel and Peel (1941) 59 examples in a series of 115 showing glycosuria.

For the purpose of this communication the term lowered renal threshold is applied to any instance in which glycosuria has been observed while the blood sugar values have not exceeded 0·17%.

In clinical practice it is seldom possible to determine the level of the threshold with exact precision. However, frequent estimations of the level of blood sugar and their comparison with the results of the usual chemical tests for glucose in urine provide a reasonably accurate guide for the satisfactory management of patients. It is necessary to remember the fallacies of urine testing with Benedict's and Fehling's reagents and to ensure that the reducing substance in urine is in fact glucose.

As far as is known there is no relationship between a lowering of the renal threshold to glucose and the development of *diabetes mellitus*. Confusion may arise, however, because they possess two features in common: they are both associated in the finding of sugar in urine by the usual chemical tests and they may both exhibit hereditary tendencies. The fact that the two conditions can occur simultaneously in the one patient is not well appreciated. Few authorities mention the association of the two conditions, although Russell Wilder (1941) states:

> The threshold in *diabetes mellitus* is usually normal . . . occasionally, but rarely, a low threshold is found. Sugar may be excreted continuously under these circumstances, even when enough insulin is given to maintain the blood sugar at values well within the normal range, and hence the qualitative tests of urine, on which ordinarily such large dependence is placed as a guide to management, are no longer helpful and frequent determinations of blood sugar must be made to determine the dose of insulin.

In similar vein R. D. Lawrence (1947) writes:

> A low threshold is not uncommon in true diabetes and leads to more dramatic trouble. In these cases glycosuria persists even when treatment has reduced the blood sugar to normal levels. I have seen several such cases in which too much insulin has been given and severe hypoglycæmia produced in a vain and dangerous attempt to make the urine sugar free. Such experiences point the necessity of blood sugar estimations and the importance of knowing the threshold.

In my experience the association of the two conditions is not uncommon and six new examples have come under my notice in the past twelve months. The youngest patient I have yet seen was a boy, aged fifteen years, while the oldest was a woman aged seventy-two. The longest association of the two conditions is that of a man, now aged forty years, who has been under treatment for diabetes for the past twenty-three years. A lowered renal threshold was determined at the onset of diabetes and as far as can be ascertained the level of his renal threshold to glucose (which is approximately 0·12%) has not changed appreciably since 1929. Broadly speaking the patients encountered in practice fall into one of two groups—those who are known to have a lowered threshold and at a subsequent date develop diabetes, and those who develop diabetes and because of their unusual response to treatment are then found to have a lowered threshold. A few case histories will serve to illustrate some of the problems which arise. The following two examples are quoted in order to show by contrast the dangers of relying on urine tests as a guide to the management of diabetes when the renal threshold to glucose is already known to be low before treatment is instituted.

J.M.H., a married female, aged thirty-eight years, noticed some fatigue and thirst associated with the loss of a stone in weight during the early part of 1951. Her past history was clear, apart from an operation for retroversion and appendicectomy. She has three healthy children aged eleven, seven and two years, the confinements being uneventful. Her father suffers with *diabetes mellitus*. In 1947 during the course of a routine medical examination glycosuria was discovered and a glucose tolerance test was performed which suggested the presence of a lowered renal threshold. This was confirmed by a second test a year later.

Blood sugar:	July 1947	June 1948
Fasting	0·10%	0·10%
½ hour after 50 gr. glucose ..	0·21%	0·15%
1 " " " ..	0·20%	0·15%
1½ " " " ..	0·12%	0·13%
2 " " " ..	0·08%	0·10%

On each occasion the fasting urine was reported to contain a trace of reducing substance and the urine samples at one and at two hours contained approximately 2% of glucose. After the development of symptoms another glucose tolerance test was performed in August 1951 and gave this result:

Blood sugar:	
Fasting	0·13%
½ hour after 50 gr. glucose ..	0·18%
1 " " "	0·26%
1½ " " " ..	0·21%
2 " " " ..	0·17%

The fasting urine contained an appreciable amount of glucose, as did the subsequent samples obtained during the test. A diagnosis of *diabetes mellitus* with a lowered renal threshold was made upon the results of the blood tests and the history of fatigue, loss of weight and thirst. The patient was admitted to hospital and stabilized on an appropriate diet with one mixed injection of 12 units regular insulin and 12 units protamine zinc insulin given each morning before breakfast. During her ten-day stay in hospital the urine tests for sugar were not regarded as any indication of her progress and in fact only two tests showed no reduction to Benedict's solution. Blood sugar estimations were performed frequently and her condition was considered stabilized when the results of tests made at 8 a.m., 10 a.m., 12 m.d., 2 p.m., 4 p.m. and 6 p.m. all lay within the limits of 0·10% and 0·18%. Her symptoms rapidly subsided, she gained weight and suffered no hypoglycæmic reactions. Since discharge from hospital she has remained well and is quite capable of leading a normal life. Blood sugar estimations made at 11.30 a.m. and 4.30 p.m. on several occasions since she left hospital have always yielded satisfactory figures.

R.O., a married male, aged thirty-one years, first came under my care in 1949. His early history was of no significance and there was no family history of *diabetes mellitus*. He enlisted in the Armed Services in 1937 and after an air crash in 1941 glycosuria was observed. Glucose tolerance tests were performed and he was told that he had a lowered renal threshold and was allowed to continue his service. He remained in good health until the early part of 1948, when he noticed a progressive loss of weight together with tiredness, thirst, polyuria and weakness. These symptoms progressed over a period of four months and he was then invalided for investigation. A glucose tolerance test was performed and he was told that he had developed *diabetes mellitus*, was discharged from service and was admitted to hospital for treatment. He remained under observation for eleven weeks while attempts were made to stabilise his condition with insulin. He kept most careful records of his urine tests, which were made four times each day, but despite various modifications of diet and insulin dosage the tests seldom gave sugar-free results. During this period he suffered from severe and unexpected hypoglycæmic reactions which gave him no warning. Eventually he was discharged and soon after he suffered from repeated reactions in which he became violent, abusive and aggressive. These resulted in the loss of his employment and in provoking a grave breach of both domestic and marital relationships. He was again admitted to hospital and once more remained for many weeks, but with no greater success in producing urine which was clear of sugar. During both periods in hospital a few blood sugar estimations were made haphazardly. However, despite the fact that he had been proved to have a low threshold seven years previously, no heed was paid to this. He was eventually discharged from hospital a second time and again suffered from violent hypoglycæmic reactions, menacing himself and others. When first seen by me after one severe episode of hypoglycæmia, he was depressed and almost suicidal and regarded himself as "finished". At this stage his insulin dosage was 36 units of regular insulin and 32 units of protamine zinc insulin given as a mixed injection before breakfast. In a purely empirical fashion this was at once reduced to 16 units of each type of insulin and he was admitted to hospital for observation. Every sample of urine obtained from him produced a heavy reduction of Benedict's solution; the reducing substance was shown to be glucose. After five days in hospital without any alteration in insulin dosage a series of blood sugar estimations was made while the patient was out of bed and exercising normally. The following figures were obtained:

6 a.m.	0·22%		
8 a.m.	0·24%	7 a.m. Insulin	7.30 a.m. breakfast
10 a.m.	0·20%		
12 m.d.	0·07%		
2 p.m.	0·16%	12.15 p.m. luncheon	
4 p.m.	0·15%		
6 p.m.	0·19%	4.45 p.m. dinner	

All urinary samples which were taken at hourly intervals during the test showed reduction to Benedict's solution. A morning tea with a carbohydrate value of approximately 30 grammes was added to his diet to prevent any reaction in the later part of the morning and he was discharged from hospital six days after admission, it being thought undesirable to keep him longer because of his previous unfortunate experiences. He soon found appropriate employment and has been working ever since. He has remained well and reports for review at intervals of four months, when a series of blood sugar estimations is made throughout a day and minor adjustments are advised in insulin dosage, if these are indicated.

In many instances the existence of a lowered renal threshold to glucose is unknown when treatment of diabetes is first instituted. Suspicion should be aroused when appropriate treatment is followed by repeated insulin reactions which are associated with intermittent or continuous glycosuria. The following two case histories illustrate some of the difficulties which may be encountered.

M.D., a married female, aged twenty-three years, was first seen in April 1951. Her previous history was of no significance, but several of her father's cousins suffer with diabetes. At the age of fourteen years she developed *diabetes mellitus*, the history of onset being quite typical. She was admitted to hospital and her condition became stabilized on two injections of regular insulin each day (25 units before breakfast and 16 units before dinner). She remained well for six years, although her urine tests often revealed the presence of sugar. She then suffered an attack of gastro-enteritis and her diabetic stability was disturbed. She was admitted to hospital and strenuous efforts were made to free her of glycosuria. She was eventually discharged, taking 30 units of regular insulin twice

daily, but this was gradually reduced to the former dose. She remained reasonably well, but often suffered from hypoglycæmic reactions and usually showed some sugar in the urine. In 1950 with a change of medical advice a further attempt was made to deal with her glycosuria. Various types and combinations of insulin were tried and she spent much time in hospital. These efforts produced more and more hypoglycæmic reactions and her confidence in her ability to lead a normal existence became seriously undermined. She became frightened to leave her home unattended for fear of collapsing in the street; while the nights were frequently disturbed by reactions which occurred during sleep. On the occasion of my first interview it was suggested to her that she should again enter hospital for observation as her history was suggestive of a lowering of the renal threshold. To this she reluctantly agreed, saying that all this had been done before with no benefit. When admitted to hospital she was taking 20 units of regular insulin in the mornings and 18 units of regular insulin in the evenings. A series of blood sugar estimations were performed but proved of no assistance as she had a marked hyperglycæmia, all values obtained being above 0·30%. She was then transferred to a single injection of mixed insulins (24 regular and 16 protamine zinc) given before breakfast. After some days on this dose another series of estimations gave the following results:

6 a.m.	0·06%		
10 a.m.	0·19%	7 a.m. insulin	7.45 a.m. breakfast
12 m.d.	0·12%		
2 p.m.	0·18%	12.15 p.m. luncheon	
4 p.m.	0·15%		
6 p.m.	0·18%	4.45 p.m. dinner	

With the exception of the fasting specimen which contained no sugar, all samples of urine obtained throughout the day gave a heavy reduction of Benedict's reagent. Glucose was isolated from the urine. She showed a definite sensitivity to small variations in the ratio of regular and protamine zinc insulin in the various mixtures which were prescribed. As she lived in another State, she was discharged to a relative's home and encouraged to lead a normal domestic life. Eventually she was allowed to return to her own home on a dosage of 16 units regular insulin and 20 units protamine zinc insulin. She was instructed to cease testing her urine. She has reported by letter at intervals and she is now leading a normal life, is feeling well, and has had only one slight reaction in the past eight months. A series of blood sugar estimations made in December 1951 gave quite satisfactory results.

10 a.m.	0·14%
12 m.d.	0·08%
2 p.m.	0·15%
4 p.m.	0·09%

H.L.B., a married female, aged forty-nine years, was first seen in September 1951 complaining of thirst, tiredness and loss of weight which had been noticed for the previous eight weeks. There was no family history of *diabetes mellitus*. The past history was clear, apart from two attacks of pyelitis, one in 1936 and the other in 1949, both of which responded rapidly to appropriate therapy. There was no information to suggest previous glycosuria. The urine was found to contain a large amount of glucose and some acetone and the diagnosis of diabetes was confirmed by finding a fasting blood sugar value of 0·23%. She was admitted to hospital for stabilization and received an appropriate diet with one injection of mixed regular and protamine zinc insulins each morning before breakfast. Benedict's tests were performed on the fasting sample of urine and on samples obtained after each meal and at bed time. Heavy glycosuria persisted and the insulin dose was raised at intervals of three days. On the tenth day after commencing treatment she complained of weakness and tiredness, particularly in the later part of the day, and did not appear to be making the usual response to insulin therapy. She then suffered from two frank hypoglycæmic attacks on two successive days, both of them in the late afternoon. Her urine tests at this stage still showed an appreciable reduction of Benedict's reagent. The insulin dose was halved and two days later she felt appreciably better. A series of blood sugar estimations was then made and gave the following results:

10 a.m.	0·20%
12 m.d.	0·17%
2 p.m.	0·12%
4 p.m.	0·11%

Samples of urine were obtained each hour throughout the period of the test and all showed an appreciable reduction of Benedict's reagent. The urine tests were immediately abandoned as a means of assessing the insulin dosage and further blood sugar estimations were performed when necessary. She promptly made a rapid symptomatic improvement and has remained well ever since.

These two case histories are presented to show, by contrast, that the repeated finding of glycosuria in diabetic patients who show clinical evidences of hypoglycæmic reaction while under close observation, should always raise the question whether the renal threshold to glucose is lowered.

CONCLUSION

In clinical practice it is difficult to correlate glycosuria and glycæmia exactly. However, frequent examinations of the urine and estimations of the blood sugar throughout a day will provide a sufficiently accurate means of proof that the renal threshold is below the accepted limit of normality (0·17%).

The occurrence of hypoglycæmic reactions with persistent glycosuria is unusual and should suggest investigation of the renal threshold of any patient presenting this problem.

Just as the diagnosis of *diabetes mellitus* must invariably rest on blood sugar analysis, so treatment should be controlled by the same means.

SUMMARY

The occurrence of a lowered renal threshold to glucose in patients suffering from *diabetes mellitus* is not uncommon. Such cases may present themselves in one of two ways. A patient already known to have a low renal threshold may develop diabetes at some later date. Secondly a patient suffering from proven *diabetes mellitus* may experience hypoglycæmic

reactions with insulin therapy in spite of persisting glycosuria.

Case histories are presented illustrating both types of patient.

The successful management of these patients is possible only if the condition is recognized and blood sugar estimations are made the basis for control.

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A REVIEW OF CASES OF POLYARTERITIS NODOSA: WITH SPECIAL REFERENCE TO THE PATHOLOGY[1]

J. D. HICKS AND D. C. COWLING

" O, what may man within him hide
Though angel on the outward side."
MEASURE FOR MEASURE, III, 2.

SEVERAL patients suffering from *polyarteritis nodosa* were treated in the Royal Melbourne Hospital during the last two years. These cases are of interest, because so few of them resemble the older classical descriptions and because the macroscopic appearance of the affected tissues may give little assistance in the diagnosis. An awareness of these facts may bring to light further cases.

HISTORICAL

The first case was described by Rokitansky (1852) and the pathological appearances were recorded by Kussmaul and Maier in 1866, but, by the beginning of the century, only five cases had been reported (Osler, 1907). Most of the earlier workers considered that the process was syphilitic. By 1917, this idea was finally rejected and at this time Klotz (1917), as the result of clinical observation and animal experiment, considered that streptococci were the causal organisms.

In 1925, Gruber put forward the conception that the condition was a manifestation of the reactive processes in hypersensitivity. He stated: " We regard periarteritis nodosa as the expression of a constant characteristic reactive process of the arterial system in the manner of an hyperergic phenomenon during the course of very different infectious-toxic diseases. This is hypothesis." However, American workers during this period and still later comparing the lesions seen to those in typhus, Rocky Mountain spotted fever, and other epidemic diseases which were coming to notice in animals at that time, considered that the condition was probably due to a virus infection (Harris and Friedrichs, 1922; Haining and Kimball, 1934).

More recently, the finding of a number of cases, coincident with the advent of sulphonamide therapy which seemed to be incriminated as a causal agent, made more obvious the possible association with a hypersensitivity mechanism as the background of the disease (Lederer and Rosenblatt, 1942).

The term " collagen disease " was introduced by Klemperer, Pollack and Baehr in 1942. They considered that connective tissue proper could be regarded as a functional biological unit and used the term " collagen disease " for conditions where connective tissue was diffusely involved. Originally, they considered that *lupus erythematosus* and scleroderma only should be considered such diseases, but subsequently, although Klemperer (1950) throws doubt on the desirability of this, the term has been used to cover also rheumatoid arthritis, rheumatic fever, dermatomyositis, *polyarteritis nodosa* and perhaps glomerulonephritis.

CLINICAL FEATURES

It is not intended to deal in detail with the clinical features. It suffices to say that the diagnosis is most difficult because of the protean symptoms and the variable findings dependent upon the degree of involvement of each particular system. The diagnosis may be confirmed during life by muscle and skin or perhaps even a lymph node biopsy. A table giving a brief summary of the clinical picture is provided. Among the eight proven cases which were studied, two patients recovered.

PATHOLOGICAL FINDINGS

Macroscopic Appearances

The subcutaneous and muscle nodules often described were not found in any of the cases seen *post mortem*, although these were present in two cases in which improvement occurred. Such evidence of isolated medium-sized arterial involvement as aneurysm and rupture was also not seen. The picture was rather of gross arteriolar change in viscera, producing diffuse alterations which were often scarcely discernible to the naked eye.

In the heart in three of the six cases, pericarditis was present. In one case, that of

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F.T., this was particularly gross and accompanied by a large blood-stained pericardial effusion. In two cases there was an adhesive fibrous pericarditis. There was no gross enlargement of the heart. The muscle showed no gross lesions but in one case (patient J.P.) a small recent vegetation was present on the aortic valve. In this same case there was a considerable degree of coronary atheroma of patchy distribution, as there was also in the case of C.B.

In the lungs, some congestion was evident in all cases. In the case of F.T., large firm grey-white nodules were present, up to 2·0 centimetres in diameter, scattered diffusely. Confluent nodules of this type replaced almost entirely the lung tissue of the right middle lobe.

Infarction of the spleen was present in two cases, and the spleen was moderately enlarged in three. In two cases, generalized lymph node enlargement was a prominent feature.

The appearance of the kidneys attracted attention. In two cases (patients J.B. and N.B.) there were present swelling and œdema of the cortex with a mottled pale and red colour. In the case of N.B., the cortex was speckled with small pale spots, just visible to the naked eye, which were shown to be swollen glomeruli. In another (patient F.T.) large grey-white nodules up to 0·75 centimetre in diameter were apparent. In the case of G.L. there were found some swelling of both kidneys and a fine speckling and streaking of cortex and to a less extent of medulla with yellowish soft areas, the appearance on first sight suggesting pyelonephritis with small abscesses. It was subsequently seen that these were arterial lesions. In the case of J.P., a fine cortical stippling with grey flecks was also

TABLE I
Clinical Summary of Cases

Name.	Age. (Years.)	Sex.	Duration; Outcome.	Remarks.	Drug or Other Factor.
C.F.	53	F.	1 month; died.	Following pyelolithotomy was given sulphamethazine. She rapidly developed malaise, fever, and a rash which became generalized.	Sulphonamides.
L.H.	25	M.	1 month; improved.	Presented with malaise, muscular pain and tender nodules in muscles. Later some hæmaturia occurred, but the patient's condition improved.	
N.R.	29	F.	4 months; improved.	Swelling of glands in neck followed by diarrhœa and vomiting were first symptoms. The glands were proved to be tuberculous. Six weeks later the patient developed tender red subcutaneous nodules resembling a severe grade of *erythema nodosum*.	Bacterial sensitivity.
F.T.	18	F.	1½ months; died.	Illness commenced with malaise and conjunctivitis. Three weeks before death, fever, malaise, pleurisy with cough occurred with no response to chemotherapy and antibiotics. The patient developed phlebitis of a leg, and terminally a pericarditis.	
J.P.	61	M.	2 months; died.	For two preceding winters, pneumonia, treated with sulphonamides, had occurred. The patient again developed pneumonia, treated with sulphonamides and antibiotics. He rapidly developed a hæmorrhagic papular rash, lymphadenopathy and œdema. The œdema persisted, gross albuminuria being present, and then a transient attack of auricular fibrillation occurred. He developed severe melæna, became uræmic and ran an intermittent high fever and died.	Sulphonamides.
C.B.	37	M.	1 month; died.	He had recurring tonsillitis for some time treated with sulphonamide. Illness commenced following tonsillectomy during which sulphadiazine was given. He developed an urticarial rash and joint pains, then pleuritic pain and dyspnœa. There was later lymphadenopathy and a macular erythematous rash. Cyanosis and clubbing of the fingers became marked. Albuminuria persisted, and his condition deteriorated and he died suddenly, despite ACTH administration.	Sulphonamides.
N.B.	38	M.	2 months; died.	Illness commenced with lassitude, anorexia and hæmaturia; the patient was never œdematous. He vomited persistently, became uræmic, and died suddenly. He had worked in a moulding shop for years and had silicosis.	
G.L.	71	F.	? 2 months; died.	Had a goitre for fifty years with no symptoms until several months before admission to hospital, developed dyspnœa on effort and œdema of ankles. There was, when admitted, congestive cardiac failure with auricular fibrillation and basal metabolic rate of more than +44%. Methyl thiouracil was given and she had several febrile attacks, considered to be thyroid crises; she went downhill over a period of a month, gangrene of the fingers occurring before death.	Methyl thiouracil.

seen, although the typical glomerular lesions were not present.

In one case (patient J.P.) the ileum showed œdema, bleb formation, large areas of ulceration and hæmorrhages into the mucosa.

There was gangrene of the fingers in one case (patient G.L.) with an acutely inflamed radial artery and thrombosis in the digital vessels, shown to be due to polyarteritis, while in another case, that of C.B., clubbing of the fingers was present.

Microscopic Appearances

Heart.—Five out of six cases showed in some degree changes ascribable to polyarteritis. There was patchy infiltration with cells, mainly of the small round cell type, around arterioles and capillaries and between muscle fibres. There was some degree of fibrosis, sometimes minimal in amount, replacing muscle fibres in a number of sections, but this may have been due to previous ischæmia. The muscle fibres at times showed changes such as slight swelling, or shortening and poor staining of their sarcoplasm. The nuclei were often irregularly swollen and deeply stained. In one case there was a considerable fragmentation of muscle fibres. Apart from the changes in and about arterioles, in two cases a segment of the wall of a major coronary vessel was necrotic in all coats and infiltrated with leucocytes, both small round cells and polymorphonuclear leucocytes and with perivascular accumulation of such cells. The lumen was slightly narrowed and in neither instance was there thrombosis. In all cases some pericardial changes were present, generally a dilatation of the subserous capillaries and mild infiltration with lymphocytes and mononuclear cells. The serosal cells were swollen and cuboidal in shape in some sections.

In the case of F.T., a thick fibrinous exudate was partly organized, with accumulation of leucocytes. Some fibrosis of the epicardial fat, with small areas of leucocytic infiltration, was evident in two cases.

Striated Muscle.—Striated muscle was examined in only one case, an area of damage being found. Muscle fibres were thinned, fragmented, and stained more heavily with hæmatoxylin. A few fibres showed bulbous swelling with large or multiple nuclei, probably muscle giant cells. There was an accumulation of cells about some small vessels as well as about the focus of necrosis.

Lungs.—In five out of six cases, characteristic changes were present in the lungs. In the other case (patient N.B.), owing to the presence of accompanying silicosis, the picture was not characteristic but, nevertheless, there were some features closely resembling those of the other cases. In the smaller arteries and arterioles there were scattered areas of necrosis and infiltration with leucocytes and perivascular collections of such cells (Figure I). The lumen was often greatly narrowed and,

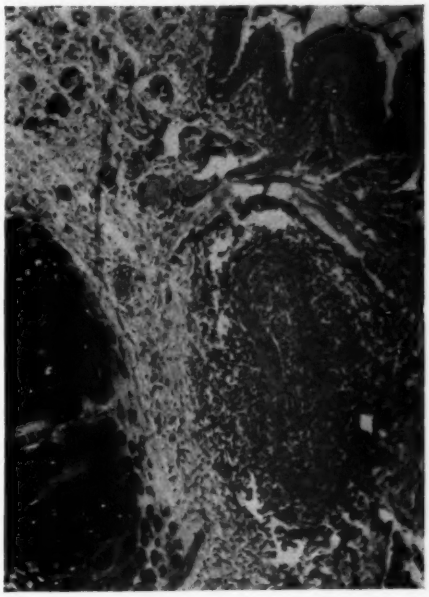

FIGURE I

Photomicrograph of wall of bronchus in the case of G.L. Lumen and bronchial epithelium above, ring of cartilage at lower left. Branch of bronchial artery with necrotic wall, leucocytes surrounding vessel and extending through the wall and into the intima. ×75

in some instances, thrombosis had occurred. However, in these cases there was infarction of macroscopic size in only one, that of F.T., and in this instance the areas of infarction corresponded with the grey nodules seen macroscopically. These areas were composed of necrotic lung tissue stuffed with leucocytes, mainly small round cells with a few polymorphonuclear cells.

Congestion of the alveolar capillaries and some degree of œdema of the alveoli were present in all cases. In most, minor hæmorrhages were also present, and in one instance there was extensive capillary thrombosis. With desquamation of lining cells and macrophages into the lumen in some areas a viscous exudate was formed which lined the walls of alveoli

and alveolar ducts, apparently pressed to a sharp-edged membrane by the air-column.

Polymorphonuclear leucocytes were present in the bronchioles in most instances, some extension into surrounding alveoli being found in one or two cases. In some areas small numbers of lymphocytes and mononuclear cells

FIGURE II

Photomicrograph of lung in the case of F.T. In the lower portion a large vessel is obliterated by fibroblasts with fragmented leucocytes near the intima. The exudate into the lung is organized, portion of lumen remaining in alveoli at the top. × 130

were present within alveoli. In one case gross change was apparent (patient F.T.), considerable areas of lung tissue being involved in the organization of intraalveolar exudate (Figure II).

Kidney.—In four of the five cases in which the kidneys were examined, typical lesions were present. Glomerular lesions were particularly evident. Here the appearance varied from complete necrosis and infiltration with leucocytes to the presence of hyaline change, the so-called fibrinoid material and slight cellular infiltration. There was usually considerable cellular infiltration about the glomeruli. Proliferation of the cells lining Bowman's capsule was seen, frequently producing "crescents"; and sometimes adhesions of the glomerular tuft to the capsule were present. In the case of J.P. numerous completely fibrosed and hyalinized glomeruli were present and arteries and arterioles showed thickening of their walls and narrowing of their lumen due to hypertrophy and fibrosis. The changes thus appeared arteriosclerotic, although the kidneys were of normal size. Minor degenerative changes were seen in the renal tubules between which there were patchy accumulations of leucocytes.

In the case of F.T. there were numerous groups of leucocytes and in these areas there was necrosis of tubular cells which corresponded with the grey nodules seen macroscopically. Arcuate arteries and arterioles showed typical changes.

In the case of N.B., the fine white spots seen in the cortex were considered to be the necrotic and infiltrated glomeruli. In the case of G.L., glomerular lesions were minimal, but there were severe arteriolar lesions (Figure III) which were visible to the naked eye producing an appearance suggesting pyelonephritis.

Spleen.—Microscopically, it was seen that the capsule and trabeculæ were involved; there were thickening of connective tissue,

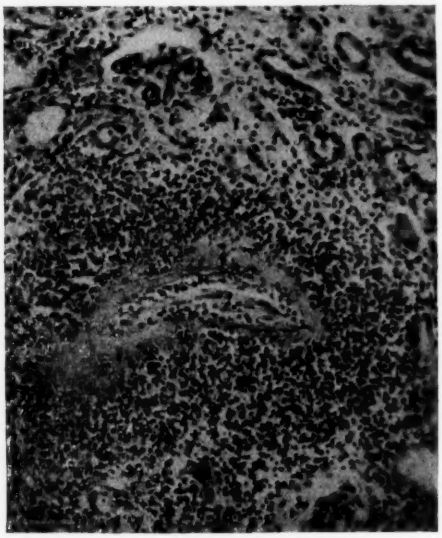

FIGURE III

Photomicrograph of kidney in the case of G.L. An artery with thickened necrotic wall, containing a few leucocytes and surrounded by a dense zone of leucocytes. Above, a relatively unaffected glomerulus. × 130

sometimes the collagen having a hyaline appearance, and infiltration with leucocytes. In some cases there was deposition of fibrin on the serosal surface, the fibrin being partly organized.

In arteries and arterioles there was a degree of change which ranged from complete necrosis of the wall with leucocytic infiltration in and about the wall to hyaline thickening of the wall. Thrombosis was evident in some vessels and infarction of small or large areas of the surrounding pulp was present in three of the five cases. In some cases there was swelling of Malpighian bodies about arterioles showing characteristic changes (Figure IV). Infiltration with polymorphonuclear cells and some fibroblastic proliferation were also seen. In some, eosinophilic polymorphonuclear leucocytes were present in moderate numbers.

Lymph Nodes.—In two of the four cases in which lymph nodes were examined (patients C.F. and N.B.) there was present a typical lesion. The most obvious feature was a hyalinization of the connective tissue in the

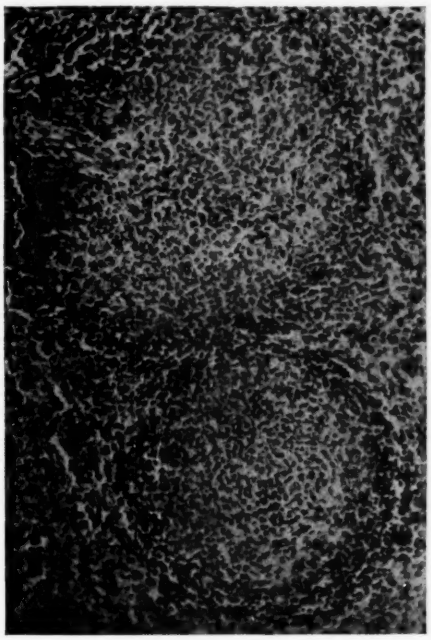

FIGURE IV
Photomicrograph of spleen in the case of N.B. Two enlarged follicles, a thickened arteriole entering the upper one. Narrow, pale fibroblastic cells are mixed with lymphocytes and polymorphonuclear leucocytes, some of which are eosinophilic. ×130

capsule and trabeculæ with focal collections of inflammatory cells. Some sinusoids had undergone a hyaline thickening of their walls, as had some capillaries, so that these structures were very prominent. There was also deposition of quite large clumps of hyaline connective tissue. The follicles also showed this hyalinization which, at an early stage, appeared as a proliferation of quite plump epithelioid fibroblasts. Typical vascular changes were not obvious. In two cases the appearance was of very slight capsular and

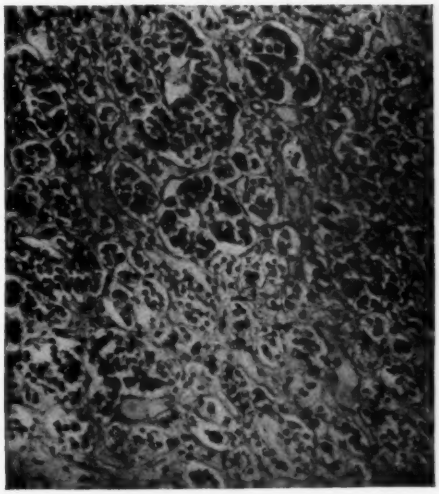

FIGURE V
Photomicrograph of pituitary in the case of G.L. Atrophy of chromophobe cells and replacement by fibrous tissue in lower portion. Groups of shrunken cells with pyknotic nuclei have fallen from the basement membrane. Nearby fields contained well preserved cell groups. ×130

trabecular changes. The sinusoids were prominent, empty, and had very slender hyalinized walls giving a lacy appearance. This appearance was not one which, without examination of the other organs, could be correlated with the disease.

Other Organs.—Skin was examined in the case of C.F. and showed typical vascular change in small vessels and some swelling and hyaline change in collagen fibres of the corium, gross leucocytic infiltration of the dermis and round vessels, ducts, and glands.

The vessels of the pituitary gland appeared to be uninvolved in the three cases in which the gland was sectioned, but in one instance there was an area of fibrosis in the anterior portion with retrogressive changes in the cells such as pyknosis of nuclei, separation of cells from the basement membrane, and granular eosinophilic staining of the cell cytoplasm (Figure V).

The stroma and vesicles of the thyroid gland were normal in two cases, but in a third, that of G.L., who had been treated with thiouracil,

medium-sized vessels in the capsule of the gland were severely inflamed in places, smaller arterioles within the gland were affected (Figure VI) and minor inflammatory changes with accumulation of polymorphonuclear and other leucocytes were present in and around vesicles within a large thyroid nodule.

The testis was examined in one case. Gross atrophy of the epithelium of the seminal tubules was observed, the interstitial cells were in prominent groups, but no inflammatory changes were seen.

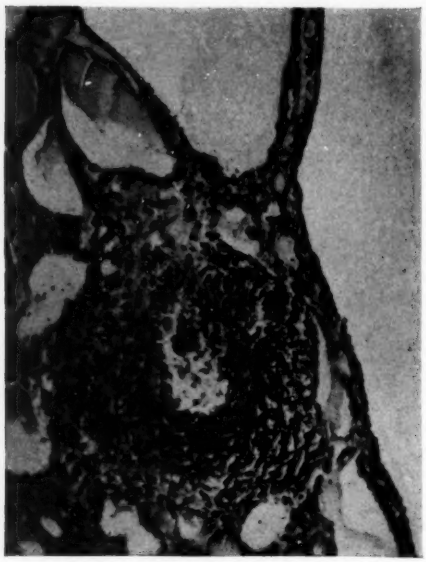

FIGURE VI
Photomicrograph of thyroid in the case of G.L. A small artery has a thickened wall disrupted by numerous leucocytes which spread out to the surrounding vesicles, some large, some small. × 130

The suprarenal gland was examined in three cases. In one case, that of C.B., who had been given ACTH without any dramatic effect, a peculiar cell picture was seen in the *zona glomerulosa* and *columnaris* of the cortex. Here many of the cells were swollen and rounded, poorly staining and with considerable vacuolation of the cytoplasm. In other cases, the gland showed no great departure from normal.

The liver in all cases showed varying degrees of cellular infiltration in portal tracts, with varying degrees of vascular change present here also.

The bowel in the case of J.P. showed gross changes. There was patchy necrosis, in some places with complete loss of mucosa down to the *muscularis mucosæ*. The mucosa and submucosa were infiltrated with cells, mainly lymphocytes and larger macrophage cells, with a few polymorphonuclear leucocytes. There were typical changes in small vessels with necrosis, thrombosis and hyaline change. The muscle showed patchy œdema and infiltration with inflammatory cells.

DISCUSSION

Morbid anatomical studies reveal basic histological similarities in the collagen diseases. Thus polyarteritis may be seen in rheumatoid arthritis, scleroderma and dermatomyositis. The variety of changes in connective tissue, blood vessels and other organs has not been studied sufficiently as yet to allow us to decide what are the common ætiological factors, and what factors are responsible for the diversity of structural change.

In the cases studied there was reasonable evidence that in five of the eight cases a definite association with a "hypersensitivity state" was present. In three, sulphonamide had been administered and all these cases were fatal. One case, that of N.B., appeared to be due to bacterial "sensitivity". From the clinical point of view it might well have been considered a severe case of *erythema nodosum*, but histological examination of a skin lesion showed changes typical of polyarteritis. Bergstrand (1950) has reported similar lesions in cases of severe *erythema nodosum*. Such a case suggests that polyarteritis is not a disease entity, but a pathological process which may result from any one of a number of exciting causes, occurring in varying grades of severity.

In one case methyl thiouracil seemed to be the exciting agent. The drug was given in somewhat larger doses than usual because of the development of what appeared to be thyroid crises. Although Marine and Baumann (1945) have described the occurrence of polyarteritis in rats fed with thiouracil, we were unable to find a reference to this complication occurring in humans.

It was of interest to note that in seven of the eight cases a differential leucocyte count revealed no eosinophilia. Such authors as Lebowich and Hunt (1940) have stressed the significance of eosinophilia in the diagnosis. Whitby and Britton (1950) state that only 12% of cases show the feature, with counts sometimes up to 20,000 cells per cubic millimetre.

There is a group of cases associated with asthma and other allergic phenomena, fever and eosinophilia. Smith (1948) reported a case, but did not regard it as *polyarteritis nodosa*

because of the presence of lung lesions. Churg and Strauss (1951) reported a group of such cases and stressed the widespread nature of the granulomatous lesions seen in them, and suggest that a separate name—allergic granuloma—be given. They quote Wilson and Alexander, who in a review of 300 cases found eosinophilia in 6% of patients without asthma, and 94% with asthma.

In a discussion of the macroscopic features of this disease the work of Davson and his colleagues deserves particular mention (Davson, Ball and Platt, 1948). They first made known generally the appearance of the kidney to the naked eye (Wainwright and Davson, 1950), describing the swollen and œdematous cortex of mottled red and yellow hue with small opaque white spots, the swollen and damaged glomeruli, which may fleck the surface. In the case of N.B., who clinically manifested a rather unusual nephritis, this appearance led to the diagnosis before microscopic examination was made. The appearance of the larger grey-white nodules in the case of F.T. was not one which is well known, nor were the larger grey nodules in lung, in places confluent, an appearance with which we were familiar.

The appearance of fine yellow spots and streaks in both cortex and medulla of what appeared to be purulent material in the case of G.L. was seen on microscopy to correspond with the numerous arterial lesions. No glomerular lesions were evident, other than in close proximity to a damaged artery.

The microscopic features are now well described, again Davson contributing much to the clarity of the picture. The appearance of the hyaline change in sinusoids and capillaries, and the presence of hyalinized fibrotic areas in lymph glands in two cases was of interest because this change had been seen in lymph glands in cases of scleroderma. The appearance was identical. In these two cases there was a generalized lymph glandular enlargement as there was in the scleroderma cases.

In the case of J.P., whose history of the acute attack was of only two months, but who on the two preceding winters had had pneumonia treated with sulphonamide, it is conjectured that the presence of many fibrosed and hyalized glomeruli, and of apparently arteriosclerotic change would be, in fact, the result of a very slow process of the polyarteritis type. Attempts have been made to classify the lesions into grades of severity by Yardumian and Kleinermann (1949). They consider that the hyalinization, fibrosis and deposition of collagenous substance represent a type of repair, replacing the damaged tissue, and where the process is slow and insidious, with exacerbations, damage progresses slowly with healing between exacerbations. Arkin (1930) and other workers have also classified lesions into stages, fibrosis being the last stage. In the case of J.P., there was no doubt that organs, other than the kidney, showed lesions typical of *polyarteritis nodosa*, and the renal lesions seen in this case, resembling arteriosclerosis, probably represented healed lesions.

In early reports, no changes were recorded in the lungs, and frequency of involvement of arteries in the lungs has varied considerably, 30% being a conservative estimate (Spiegel, 1936). In five out of six of our cases, definite lesions were observed in branches of bronchial, as well as pulmonary arteries.

Although the word " fibrinoid " has been in use for nearly sixty years (Neumann, 1896), we have tried to avoid its use in describing the microscopic appearance of the altered collagen. It is considered that it does not represent any features of the altered collagen other than its strong affinity for eosin and the slightly granular texture, which are shared with fibrin. With Mallory's aniline blue, the distinction from fibrin may be definite in some examples, but, in others, a reddish colour is developed which resembles that shown by fibrin. The necrotic fibres fluoresce strongly, with a pale green colour, when stained with a mixture of acridine orange and phosphene 3R, while fibrin is clearly of a different chemical nature and its tangled threads fluoresce with a dull brownish hue.

The chemical structure of the degenerate collagen is not known. It is probably not " fibrinoid ". Klemperer (1950) has reviewed this aspect and at present no adequate comment may be made about the nature of the so-called " fibrinoid " change.

Present views concerning the nature of *polyarteritis nodosa* and the manner in which the lesions develop are not entirely satisfying, and any attempt to assess critically the hypotheses put forward by various authors must be based upon observations and verifiable experiments.

We must first consider the actual structural changes found in the vessels. The typical lesions consist of focal changes in the walls of small arteries, but arterioles are involved in some cases. The collagen fibres of the subintima are altered to a hyaline, deeply eosinophilic band of varying thickness, which in patches may appear granular and " necrotic ". At the same time, there is an accumulation of leucocytes within the vessel walls beneath or on the

intima, where this is not replaced by hyaline material, at times in the media and in the necrotic hyaline substance, and in the adventitia or surrounding tissues. At some stages polymorphonuclear leucocytes are numerous, although plasma cells and lymphocytes predominate and may be accompanied by large mononuclear cells.

In the healing stages, disappearance of the cellular infiltration is associated with fibrosis, but in the typical early lesion varying degrees of the changes described above are found. Many authors emphasize the so-called "fibrinoid" change and the patchy or focal involvement of only portions of vessels is characteristic. The lesions are nodular and may involve the vessels of various organs—kidneys, heart, spleen, liver, gastro-intestinal tract, mesenteric vessels, muscles and lung.

Arterial changes of similar type have been observed in a great many different conditions, as will be described below. As far as one can determine, there do not appear to be any fundamental histological differences in the lesions occurring in these conditions, such as would warrant the separation of the arterial changes into different types of reaction. Our own experience with a variety of lesions tallies with descriptions and photomicrographs in the literature.

Hypersensitive States.—The production of typical *polyarteritis nodosa* lesions by Rich and Gregory (1943) in experimental animals by injections of foreign protein suggested that the reaction belonged to the group of hypersensitive phenomena. This was supported by the clinical features in many cases, particularly where the condition developed in association with treatment by drugs such as sulphonamides, or with foreign sera (Rich, 1942; Lederer and Rosenblatt, 1942). Rich (1945) demonstrated similar lesions in iodine sensitivity. Marine and Baumann (1945) recorded *polyarteritis nodosa* in rats given thiouracil; our patient, G.L., had received much thiouracil. Bergstrand (1950) has suggested that hypersensitivity to bacteria or bacterial products may be an important factor and that drugs may accentuate this sensitivity.

Hypertensive States.—Acute arterial necrosis has been produced in the renal vessels of the rat by the simple raising of intraarterial pressure. Byrom and Dodson (1948) induced sudden and brief rises in arterial pressure by injection of Ringer's solution into the carotid artery and, in three days, demonstrated necrotic changes in renal vessels. Similar necrotizing arteritis in hypertension was found in the rabbit by Wilson and Pickering (1937, 1938) and in the dog by Goldblatt (1938). These authors and others (Koletsky, 1950) have indicated that the presence of renal insufficiency (not necessarily with hypertension) at least accentuates the production of arterial lesions. Smith, Zeek and McGuire (1944, 1947) list the reports of *polyarteritis nodosa* in animals as well as describing experiments of their own. In a number of cases other factors, such as infection and hypersensitivity, appear to be important, but, in the majority of instances reported, hypertension was present. In their opinion *polyarteritis nodosa* is associated with sharply rising hypertension.

Arterial necrosis has been produced by injection of pressor substances. Duff *et alii* (1939) used tyramine, Waters (1950) had used N-amylamine and also adrenaline. A clinical case of phæochromocytoma with paroxysmal hypertension in a coloured girl, nineteen years of age, was cited by Klemperer (1950).

Wilens and Glynn (1951) reviewed the clinical features of cases of *polyarteritis nodosa* and suggested that there appeared to be a group of the hypersensitivity type, but that there was a definite association with hypertension, pre-existing in many cases. We have observed cases of severe hypertension in which lesions of *polyarteritis nodosa* developed. The kidneys of an old lady of seventy-seven years of age presented the rather dramatic picture of severe arteriosclerotic vessels with scattered acute arterial necrosis and with extensive epithelial crescent formation in many glomeruli.

Miscellaneous Inflammatory States.—Askanazy (1910) described a hyaline fibrinoid degeneration in arteries in tuberculous meningitis, and (1921) acute arteritis with fibrinoid necrosis in the base of chronic gastric ulcers. We have observed these lesions from time to time. Cairns and Russell (1946) describe similar changes in arteries in pneumococcal meningitis treated with penicillin (suggesting that there is a hypersensitive basis), Helve, Pätiälä and Saxén (1951) describe "*periarteritis nodosa*" lesions in a case of sporotrichosis. Focal arterial necrosis and inflammation in the appendix have been described by Weinberg (1950), Platt (1950) and by Plaut (1951), who recorded 88 cases in which the lesions were not associated with any clinical condition of the patients. Wu (1937) showed that formation of fibrinoid material did not require a special sensitization process but could follow simple mechanical tissue injury. Similar alterations in collagen have been described in other special circumstances. Holman (1950) produced

necrotic changes in arteries in dogs with renal insufficiency by a diet with a high fat content. Such lesions were prevented by vitamin *E* in high dosage. Ham (1940) with large doses of vitamin *D* induced renal calcification, but the arterial necrosis may have followed the subsequent hypertension.

Selye and Pentz (1943) showed that the administration of desoxycorticosterone in dogs with renal insufficiency produced polyarteritis.

Old and Russell (1951) reported necrotizing arteritis confined to the lung in a case of congenital heart disease. One of us (Hicks, 1952) has observed similar lesions in a case with mitral stenosis. Parker and Weiss (1936) found necrotic changes in only occasional arterioles in cases of mitral stenosis.

From these numerous sets of conditions in which similar changes in the subintimal collagen are observed, it is apparent that an explanation of the mechanism of their production must be based upon a much wider concept than that of "hypersensitivity". One may say either that a number of different factors produce a similar change in vessel walls, or that the vessel reacts in one particular manner to damage produced in a variety of ways. Basically, there is an alteration in the structure of the tissue components, both in their chemical groupings and in their physical arrangement. Whether these changes are identical in the various conditions indicated above, or whether there are a number of specific rearrangements of the protein macromolecules cannot be determined by our present methods of analysis. Such an answer can be anticipated when we have approached the problem along fundamental lines as have been indicated by Klemperer (1950). A precise knowledge of the structure of the mucopolysaccharide-protein complex of the fibres involved and of the various enzyme systems, growth substances, hormones and vitamins affecting their formation and deformation is required. For the present little more can be said than that a peculiar and rather localized change occurs in the walls of vessels in certain sets of circumstances. The change may be the result of a breakdown of the tissue, or a combination of the tissue with damaging agents. It is important to maintain a discerning watchfulness, accepting those fragments of information which from time to time throw light on basic mechanisms but rejecting concepts lacking verifiable supporting data.

SUMMARY

Eight cases of *polyarteritis nodosa* are reported, one being associated with thiouracil therapy. It is apparent that the clinical picture of *polyarteritis nodosa* may not be at all characteristic and one must be constantly aware of the possibility of the disease to find it. However, care must be taken not to regard as *polyarteritis nodosa* all those cases showing some involvement of vessels in inflammatory processes, nor to think that the use of the label "*polyarteritis nodosa*" leads to a clearer understanding of the pathological process and of the management of an individual case.

The nature of the tissue alterations observed in *polyarteritis nodosa* is not understood and until the fundamental changes are more clearly demonstrated the exact processes concerned in the ætiology of this condition will remain obscure.

ACKNOWLEDGEMENT

We wish to express our thanks to members of the honorary medical staff of the Royal Melbourne Hospital for permission to publish data from the clinical notes of cases.

ADDENDUM

Since this article was written a report of a case of *polyarteritis nodosa* following thiouracil treatment has been published in *The Lancet* (1952, **2**, 319) by P. G. Dalgleish, who refers to four similar cases.

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EXPERIENCE WITH THE INTRAMUSCULAR ADMINISTRATION OF HEPARIN PREPARATIONS: A COMPARISON BETWEEN AQUEOUS AND RETARD HEPARIN[1]

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THE fact that heparin inhibits certain reactions in the blood clotting system has led to the clinical use of this compound in the prophylaxis and treatment of thromboembolic conditions (Jorpes, 1946). As heparin is inactivated when given by mouth, except when introduced into the sublingual pouch (Litwins *et alii*, 1951), originally it was given by the intravenous route. Two different procedures are in use for this purpose. In the one, heparin dissolved in saline is infused at a constant rate (Murray *et alii*, 1936 and 1937). In the other, a concentrated heparin preparation is injected at certain time intervals (Crafoord, 1937). The first procedure is preferable for once the heparin concentration necessary to elevate the whole blood coagulation time has been determined, a continuous supply will keep it at a desired level. A disadvantage of the continuous infusion technique is that the recipient's movements are restricted and that relatively large fluid volumes are introduced into the circulation. It may be undesirable in certain pathological states to maintain this procedure for long periods. Intermittent intravenous injection results in an immediate steep increase of the whole blood coagulation time followed by a rapid decline to the normal level. The initial blood heparin concentration is therefore maintained for a very short period.

In order to overcome the drawbacks of intravenous heparin application, other parenteral routes have been suggested. It has been observed that after subcutaneous, intramuscular and intrasternal administration of heparin the whole blood coagulation time is delayed (Jaques *et alii*, 1938; Lindgren and Wallden, 1944). Subcutaneous and intramuscular injections have been favoured by several workers (Lehman and Boys, 1940; Walker, 1945; Stats and Neuhof, 1947; Abrahams, 1950). Suggestions have been made to delay the absorption by incorporating heparin into retarding agents with and without the addition of vasoconstrictors (Bryson and Code, 1944; Loewe *et alii*, 1942; Vorzimmer *et alii*, 1948; Wald *et alii*, 1951). The reverse procedure, namely more rapid diffusion into the vascular system by the use of hyaluronidase, has also been suggested (Tuchman and Moolten, 1950). The subcutaneous or intramuscular injection of the drug would seem to have an advantage over use of the intravenous route because a heparin depot is produced in the tissues from which the drug is released gradually into the vascular system. In this manner it should be possible to maintain a constant heparin level in the circulation. Insufficient information is available to indicate the efficacy and the comparative value of the various preparations and the route of administration. It is obviously difficult to draw any conclusion regarding the value of one procedure as compared to another if no controls are available.

Heparin is used in the treatment of thromboembolic conditions, and according to Gilbert and Nalefski (1949) it increases coronary flow volume. Further recent observations indicate that heparin affects the transparency of lipæmic plasma (Hahn, 1943) and may be of value in the treatment of atherosclerotic conditions and *angina pectoris* (Graham *et alii*, 1951). The efficient administration of heparin is of practical interest and it was therefore decided to compare the activity of two types of heparin preparations. One was an aqueous solution of the sodium salt containing 5000 units per millilitre, of which 4·0 millilitres were injected. The other type, called heparin retard, contained 20,000 units of heparin in 2·0 millilitres of Pitkin's menstruum.

LABORATORY TECHNIQUE

The whole blood coagulation time, as determined by the Lee White technique, was used as a quantitative measure of heparin concentration. Two millilitres of venous blood were

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measured into glass tubes maintained at 37° C. This test depends on many factors, some of which are difficult to control, and it was supplemented by the estimation of heparin in plasma. Among the several principles applied for the assay of heparin the ability to inhibit the reaction of thrombin on fibrinogen of plasma has been used. Quick (1936) measured the heparin concentration of oxalated human plasma by observing changes in the clotting time obtained by the addition of a thrombin solution. Jaques and Charles (1941) developed an assay in which the unknown and standard heparin solutions are titrated against a system consisting of oxalated beef blood and thrombin, using a constant clotting time.

The technique which we adopted is a modification of Quick's procedure. In that technique a thrombin preparation giving a clotting time of seven seconds with control plasma is used and the delay of coagulation time due to the presence of heparin is observed and compared with that of a standard preparation. It is not convenient to work with such a potent thrombin because a small difference in clotting time corresponds to a comparatively large change in heparin concentration. The following procedure has been found to be reliable and reproducible for the estimation of heparin in commercial preparations and biological fluids.

The collection and testing of blood specimens are always done on the same day.

Nine volumes of human venous blood are mixed with one volume of a 3·8% solution of tri-sodium citrate. Cell-free plasma is obtained by centrifugation.

Half a millilitre of citrated plasma is diluted with an equal volume of a fluid containing 0·76% tri-sodium citrate and 0·7% sodium chloride to which was added heparin varying in amounts from 0·12 to 0·62 gamma per millilitre reaction mixture.

Thrombin of bovine origin is diluted with distilled water until a clotting time of 20 seconds is obtained for normal plasma under the conditions of the test.

For the estimation of thrombin clotting time 0·2 millilitre of the various reaction mixtures is kept in a water bath at 37 °C. for five minutes and then 0·1 millilitre of the aqueous thrombin solution is added. The clotting times are noted. Results of four independent assays are given in Table I.

Because of the variations in the thrombin clotting time of normal plasma, it was found advisable to average the results obtained from at least three normal donors.

When the reciprocal of the average of the above clotting times are plotted against the heparin concentration, the relationship between these two factors is represented by a straight line. The heparin concentration in the patient's plasma can then be determined from its thrombin clotting time by reference to this graph. However, if the clotting time is above sixty seconds, dilutions of patient's plasma with normal citrated plasma are made in order to bring the clotting time into the working range.

TABLE I

Thrombin Clotting Times of Heparinized Human Plasma

(Results are given in seconds)

Human Citrated Plasma.	Addition of Heparin in Gamma per Millilitre.					
	Nil	0·125	0·25	0·375	0·5	0·625
1	20	22·5	24	32	39	50
2	20	22	26	31·5	44	58
3	21	24	29	35	43	60
4	21	—	—	33	41	52

The three commercial heparin preparations were assayed by the outlined technique. The potencies did not vary by more than ±5% from each other. No standard heparin preparation was available for checking the absolute strength of the preparations used.

Monkhouse and Jaques (1950) report that a whole blood coagulation time of 20 minutes corresponds to 1·0 gamma of free heparin per millilitre of blood and a whole blood coagulation time of forty minutes corresponds to twice that quantity of heparin. These figures would be approximately twice as high if expressed in millilitres of plasma.

Our figures, as can be seen from the scattergram (Figure I), indicate that a whole blood coagulation time of twenty minutes corresponds to a concentration of approximately 1·5 gamma of sodium heparin in citrated plasma, whereas a whole blood coagulation time of forty minutes corresponds to a heparin concentration of approximately 4·5 gamma per millilitre of plasma.

The patients selected for heparin treatment were patients in the surgical and medical wards of this hospital, and were suffering from thrombophlebitis, post-operative thrombo-embolic attacks and cardiac infarctions.

METHODS

The drugs were given by intramuscular injection into the buttock or into the lateral aspect of the thigh. In some cases heparin in aqueous solution was given first and after it had disappeared from the circulation heparin retard was given at the corresponding anatomical site. In other cases the order of the drugs was reversed.

RESULTS

In the following table are summarized experimental findings in fourteen patients who obtained 28 injections of aqueous and retard heparin alternately.

It was found that of 29 intramuscular injections of aqueous preparations, 17 injections produced an effect for twelve hours; the mean period being fifteen hours. The remaining 12 were effective for less than twelve hours; the mean period being eight hours.

The results obtained by the use of heparin retard were as follows. Eighteen injections were given and in eight cases the effect lasted for more than twelve hours; the average period being fifteen hours. In ten cases the effect lasted for less than twelve hours, the average period being six hours. The figures for the actual concentration of heparin are summarized in Table III.

TABLE II

Whole Blood Coagulation Time in Venous Blood of Patients Receiving 20,000 Units of Heparin Intramuscularly
(Results are given in minutes[1])

Heparin Preparation Used.	Hours after Injection.				
	3	4	6	8	10
Aqueous	(40–50) 45	(13–51) 34	(11–50) 30	(11–63) 24	(7–38) 19
Retard	15	(12–41) 25	(14–29) 24	(8–28) 16	(8–24) 16

[1] The figures in brackets represent the variation of the whole blood coagulation time and from them the mean values were calculated.

TABLE III

Heparin Concentration in Citrated Plasma of Patients Receiving 20,000 Units of Heparin Intramuscularly
(Results are given in gamma per millilitre)

Heparin Preparations.	Hours after Injection.				
	4	6	8	10	12
Aqueous	(2·3–13·6) 5·6	(1·3–4·6) 3·3	(1·8–3·6) 2·7	(1·3–1·7) 1·5	(0·6–1·2) 0·9
Retard	(0·1–3·7) 1·8	(0·7–3·1) 1·8	(0·6–1·9) 1·3	(0·3–2·1) 1·4	

It has been observed by previous workers that there are variations in response to heparin from one person to another, and even the same person may show a different reaction when given the same amount of heparin at different times.

In view of the above facts, and in order to obtain a clear picture, it was decided to use one dosage, namely 20,000 units only, and to compare the activity of the various preparations on the same patient. A dose of 20,000 units of heparin was used because this amount does not normally give excessive prolongation of blood clotting time for long periods and is therefore more suitable for purposes of comparison than larger quantities. Effective heparinization was assumed to correspond to a blood coagulation time of more than fifteen minutes.

DISCUSSION

According to the results given in Tables II and III, the intramuscular injection of aqueous heparin produced a better effect than heparin retard of equal potency. However, in view of the fact that great variations in response have been observed, no significance can be attached to small differences. The results in the two groups are not sufficiently different to allow any conclusions to be drawn with regard to different activity of the two preparations. In individual cases aqueous heparin was found to be superior to retard heparin in ten cases,

equally effective in three cases and inferior in one case.

It appeared of interest to correlate the heparin concentration in plasma of heparinized patients with the whole blood coagulation time. This has been done in the scattergram, Figure I.

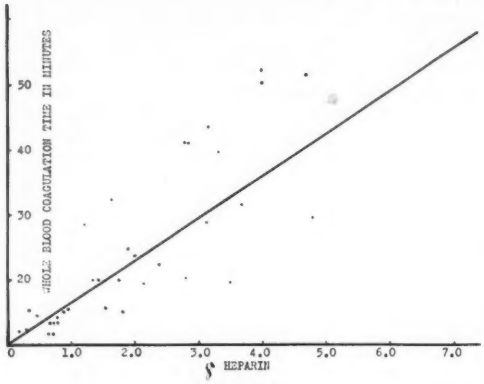

FIGURE I
Showing relationship between heparin concentration and whole blood coagulation time

From the plotted results it is quite apparent that the degree of correlation between blood coagulation time and heparin concentration is not high. This is probably due to the technical difficulties involved in the estimation of whole blood coagulation time, and also to individual variations in response to heparin. It is certainly not due to errors in the heparin assay as the graph (Figure II) indicates.

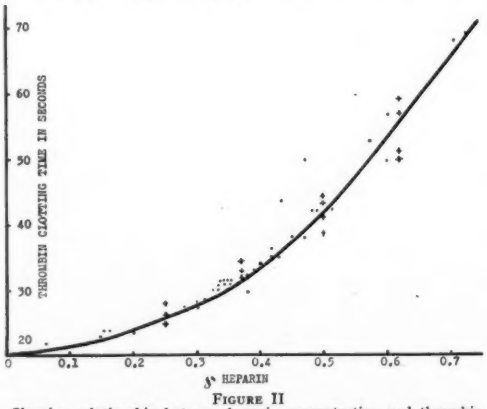

FIGURE II
Showing relationship between heparin concentration and thrombin clotting time. Dots denote heparin concentration in patients' plasma; crosses denote heparin additions to normal citrated human plasma

The figures in the graph were collected during a period of six months and show a satisfactory agreement between thrombin clotting time and heparin concentration, both in artificial mixtures and in the plasma of heparinized patients.

It was noted that in about half the instances intramuscular heparin injections caused pain at the site of the injections. This was of unusual severity in several cases. Hæmatomata were seen in two patients which made further intramuscular injections of heparin undesirable. No difference was apparent among the three heparin preparations with regard to these side reactions.

SUMMARY

A comparison of the efficacy of intramuscular injections of heparin dissolved in aqueous solution or in a gelatin medium (Pitkin's menstruum) was carried out. After the injection of 20,000 international units of the various heparin preparations, whole blood coagulation times were determined and also the heparin concentration in blood estimated. It was observed that 60% of the injections produced an effect lasting for twelve hours. The preparations containing gelatin produced results which were not significantly different from those obtained from aqueous heparin solutions.

ACKNOWLEDGEMENT

The cooperation of the clinical staffs of the Clinical Research Unit and the Alfred Hospital is gratefully acknowledged.

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THE BLOOD GROUPS OF QUADRUPLETS[1]

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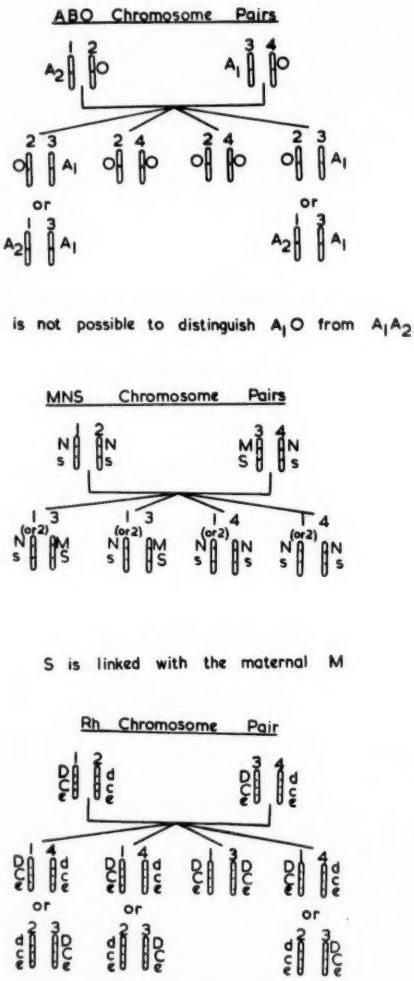
THE quadruplets born in Bellingen in August 1950 comprised two male and two female infants (Elliott *et alii*, 1951). Theoretically, these infants could have arisen in several ways: from four separate ova, from three ova with a pair of identical twins, or from two ova, each producing a pair of identical twins. Placental appearances suggested that three ova were concerned. The four infants and their parents were blood grouped in an attempt to determine which of these possibilities actually occurred. A few drops of capillary blood from each subject were added to tubes containing approximately 1·5 millilitres of sterile physiological saline. The samples were collected by Dr. Mervyn Elliott at Bellingen and forwarded to Sydney by air. Tests were performed on the day of collection, with the following results.

Father	A_2	NsNs	CDe/cde	(R_1r)	Le(a)+Lu(a)−K−Fy(a)+
Mother	A_1	MSNs	CDe/cde	(R_1r)	Le(a)+Lu(a)−K−Fy(a)+
Alison	A_1	MSNs	CDe/cde	(R_1r)	Le(a)+Lu(a)−K−Fy(a)+
Philip	O	MSNs	CDe/cde	(R_1r)	Le(a)+Lu(a)−K−Fy(a)+
Judith	O	NsNs	CDe/CDe	(R_1R_1)	Le(a)+Lu(a)−K−Fy(a)+
Mark	A_1	NsNs	CDe/cde	(R_1r)	Le(a)+Lu(a)−K−Fy(a)+

These results establish beyond doubt the individuality of each child and indicate that they have developed from distinct ova. This can be seen from the sexes and ABO groupings, from the sexes and the MN groupings, or, disregarding sexes, from the ABO and MN groupings.

The inheritance of various blood group systems is well illustrated in this family, and an attempt is made in the figure to demonstrate that of three systems. The chromosome pairs have been arbitrarily numbered one to four in the parents, and the member of each pair appearing in the children is indicated by the same number. It was not possible with the sera at our disposal to distinguish between the genotypes A_1O and A_1A_2. The MNS chromosomes of the father are identical, but the S gene, situated on the same chromosome as the MN genes, is obviously associated with the maternal M (Sanger *et alii*, 1948). It is, of course, possible that the Rh genotype of one of the parents is CDe/cDe instead of CDe/cde as shown in the figure. In the absence of anti-d serum these two genotypes cannot be distinguished serologically and the phenotypes



of the children do not assist in deciding the point. However, cde occurs fifteen times more frequently in the white population than does cDe.

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As both parents are Lewis (Le(a)) positive, Le(a) must exist in the homozygous (Le(a)Le(a)) state because anti-Le(a) acts only on homozygous individuals (Race *et alii*, 1949). The children must therefore all give positive reactions with the Le(a) serum. The Lutheran (Lu(a)) groups, being negative in both parents, must also be negative in the four children (Callender and Race, 1946), and the same applies to the Kell (K) group (Sanger *et alii*, 1949). One or another or both parents could be heterozygous in respect to the Duffy(Fy(a)) groupings, but a negative reactor amongst the children could occur only if both were heterozygous (Cutbush and Mollison, 1950).

SUMMARY

Blood groups of the Bellingen quadruplets show that the children have developed from four separate ova.

ACKNOWLEDGEMENTS

The author wishes to acknowledge his indebtedness to Dr. Mervyn Elliott for permitting this investigation and for forwarding the blood samples.

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DUODENAL INTUBATION IN DIAGNOSIS[1]

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In 1919, Lyon introduced duodenal drainage to the field of clinical investigation, especially in relation to biliary tract disorders. The description of the responses to the introduction of solutions of magnesium sulphate, of A, B, and C types of bile caused considerable interest. However, after the introduction of cholecystography by Graham and Cole in 1924, duodenal intubation as a diagnostic measure in biliary tract disorders fell into disrepute *pari passu* with advances in cholecystographic technique. In 1936 Agren and Lagerloef of Stockholm used duodenal intubation to study the effect of secretin upon pancreatic secretion in man. A commercial preparation of secretin became available in Sweden so that in 1939 Lagerloef proposed the intravenous use of secretin with duodenal drainage as a clinical test of pancreatic function. These Swedish workers introduced an important refinement in technique, namely the use of a double lumen tube, whereby the duodenal and gastric contents could be aspirated and collected separately. This enabled accurate quantitative estimations to be made of the bicarbonate and enzyme concentration of the alkaline duodenal aspirate, uncontaminated by a variable admixture of acid gastric secretion, a factor which had rendered previous estimations invalid. Subsequently the analysis of duodenal aspirate in response to intravenously administered secretin was adopted as a test of pancreatic function by clinics in the United States after the initial publications of Diamond and Siegel (1939, 1941) and of Comfort and his group (1940) and the large-scale manufacture of a reliable commercial preparation of secretin (Wyeth).

The object of this communication is to show the possible value of duodenal intubation in diagnosis in suspected pancreatic and biliary disorders, when nothing short of laparotomy will otherwise give a definite answer. Experience has been gained in slightly over fifty cases of patients suffering from a wide variety of disorders seen at the Gastro-Enterology Unit, Royal Prince Alfred Hospital, Sydney, during the eighteen months ended March 1952. Summaries of eleven illustrative cases are given in the appendix.

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Technique of Intubation

Much of the assumed difficulty in the passage of a duodenal tube has resulted from repeated failures with Miller-Abbott or other tubes in cases in which intestinal obstruction of some degree is present, with paralytic ileus, gross gaseous distension distorting the position of the stomach, nausea, vomiting and rushes of reverse peristalsis. In cooperative, fasting and non-obstructed patients, duodenal intubation has proved simple and easy. Only two attempts were unsuccessful, one in a patient with organic obstruction at the pylorus and the other in a frail elderly woman who complained of distress after fifteen minutes and before the tip of the tube was well within the duodenum.

Although a standard Miller-Abbott tube can be used, experience has been gained with a modified Shay, Gershon-Cohen, Fels four-lumen tube (diameter 6·0 millimetres, compared with 4·5 millimetres, the diameter of an ordinary Levine tube). The distal end of the tube is weighted with a condom tip containing two millilitres of mercury. In a satisfactory position, one lumen of the tube communicates with a distal balloon at the junction of the second and third parts of the duodenum; another lumen connects with a proximal balloon at the junction of the first and second parts of the duodenum; the third lumen opens between these two balloons and so drains the second part of the duodenum, whilst the fourth lumen opens proximal to the proximal balloon and so drains the stomach separately (Figure I). After a twelve-hour fast, the tube is passed *per os* in the ward, the patient lying on the right side. The patient immediately walks or is conveyed to the X-ray screening room. In 50% of the cases the tube tip is already well within the duodenum and inflation of the distal balloon will carry the tip to the third part of the duodenum. In others, it is necessary to make the patient lie on the right side, and wait, sometimes assisting peristalsis by suggesting succulent morsels of food (Andrew,

1950) until the tip passes into the duodenum. A little sedative may help in apprehensive patients. In no case was the time required longer than one and a quarter hours. When the distal balloon is in the third part of the duodenum, the proximal balloon is inflated and slack drawn out of the stomach, under screening control, so that the proximal balloon remains within the first part of the duodenum. On return to the ward, the patient lies supine with one pillow and connexion tubes are attached to the free end of the tube, connecting with a continuous negative pressure of twenty inches of water (by electric pump or by Wangensteen's apparatus).

FIGURE I
Showing duodenal tube in position with proximal balloon inflated in the first part of the duodenum

PANCREATIC FUNCTION TEST

In practice the suspicion may arise that the pancreas could be the site of primary disease in dyspepsias of vague definition with negative physical and radiological signs, in cases of recurrent abdominal or epigastric pain, in various types of post-cholecystectomy syndrome, and in some cases of wasting, malnutrition, diarrhœa or steatorrhœa. However, in chronic pancreatic disease there is no one screening test to confirm or deny such a possibility comparable to estimations of the serum or urinary enzyme levels in cases of acute pancreatitis.

Many of the manifestations of chronic pancreatic disease, such as *diabetes mellitus* and obvious steatorrhœa, are evidence of advanced disease. The serum enzyme concentrations are not usually abnormal, and their response to a variety of pancreatic stimulants, separately or together, secretin, morphine, "Prostigmin" or "Mecholyl", have been propounded recently in many publications without, as yet, any satisfactory outcome. The power of the stool to digest the gelatin of an X-ray plate has been shown to depend as much on bacterial activity as on trypsin content. Estimations of fæcal fat on isolated specimens are recognized to be unreliable in the diagnosis of steatorrhœa (Case III), and the ratio of split to unsplit fat in the stool depends rather on bacterial activity in the colon than on pancreatic lipase activity. Radiology may, however, show calcareous degeneration, enlargement of the duodenal loop, displacement of viscera or obstruction at the duodeno-jejunal junction from space-occupying or infiltrating lesions of the pancreas, but such signs are not uniformly demonstrable. Under these circumstances in the absence of an easy and reliable test to incriminate the pancreas as the site of chronic disease, duodenal aspiration can give valuable information about pancreatic function without recourse to laparotomy.

It is well recognized that secretin has a "hydrelatic" effect upon pancreatic secretion, namely it induces the gland to secrete an increased volume of juice of high bicarbonate content compared with the resting state. The response in volume and bicarbonate to secretin injected intravenously is the basis of the secretin test. The secretion of pancreatic enzymes on the other hand appears to be under nervous rather than hormonal influence; both vagal and sympathetic stimulation produce an "ecbolic" effect, a lesser increase in amount of juice, but of considerably higher enzyme concentration, sympathetic post-ganglionic fibres to the pancreas being cholinergic (Babkin, 1944). Thus the efficiency of pancreatic function may be assessed by estimating the enzyme concentration of juice collected before and after stimulation of the gland by the parasympatheticomimetic drug, "Mecholyl" (Baumann, 1949).

In the pancreatic function tests by duodenal intubation reported here a combination of the above procedures has been used. The resting duodenal juice was aspirated for twenty minutes, an intravenous dose of secretin, one unit per kilogram of body weight, given, and the subsequent juice collected in three separate ten-minute samples. The volume of all specimens was measured and the bicarbonate content estimated according to the method of Van Slyke.

The volume response to secretin is difficult to assess in view of changes in the volume aspirated according to the posture of the patient, the

diameter of the tube, the efficiency of the suction apparatus as well as the fact that secretin induces an increased flow of bile from the liver in the normal, and its volume aspirated along with pancreatic juice from the duodenum is modified according to whether the gall-bladder is normal in function, is the seat of chronic disease, or has been previously excised.

The bicarbonate response shows a wide variation among normal individuals, and in any one case the functional reserve of the pancreas is great; however, a maximum value of 80 milliequivalents per litre has been taken as the lowest limit of normal, in accordance with the observations of Dreiling and Hollander (1950).

In view of the large functional reserve of the pancreas, quantitative estimations of enzyme concentrations on the fasting juice were performed as an additional check. The fasting juice was collected into tubes in a beaker of ice, and amylase and lipase concentrations were performed according to the method of Free and Myers (1943); and the figures quoted by Baumann (1949) using this method, on a large series were accepted, namely lipase eight units, and amylase four units, as the lowest concentration compatible with normal pancreatic function. In every case either with normal or abnormal pancreatic function, there was complete agreement between the interpretation of the fasting enzyme concentration and the bicarbonate response to secretin.

The patients referred for pancreatic function tests mainly comprised those suffering from abdominal pain of obscure origin—where other investigations short of laparotomy had revealed no organic lesion. Of twenty-seven patients in this category, only four were demonstrated by duodenal intubation to have primary pancreatic lesions which were confirmed at laparotomy (see Cases I, II and IX). In no case in which normal pancreatic function was demonstrated by this means did the subsequent clinical course of laparotomy shed doubt on the validity of the test. In one case, a young woman with severe epigastric pain, in whom duodenal intubation showed normal pancreatic function, laparotomy revealed a deep lesser curvature gastric ulcer adherent to the pancreas, which had been missed on repeated radiological examinations.

In reviews of the symptomatology of primary pancreatic disease it has been repeatedly stressed that patients with pain and discomfort of pancreatic origin are often classified as suffering from a "functional" condition and given over for psychiatric care in the earlier part of their illness owing to the absence of physical signs and the completely negative result of laboratory investigations, the disease being recognized later only when a palpable mass, jaundice or ascites appears. It would appear that duodenal aspiration can be of value in these cases, when severe pain presents without obvious cause, and when the possibility of primary pancreatic disease must be excluded. Case I tells the story of a woman with severe pain who had been seen by many practitioners and labelled as "non-organic" after many negative investigations; duodenal aspiration showed a definite deficiency of pancreatic function and laparotomy revealed a chronic pancreatitis, the patient having marked although not complete relief of pain following splanchnicectomy. Case II gives a similar story in which the symptoms were due to an inoperable carcinoma of the body of the pancreas. Case III illustrates the situation in reverse, in which an hysterical type of woman complaining of recurrent severe abdominal pain obtained no relief from cholecystectomy; she later developed *diabetes mellitus*, and was found to have a total fæcal fat content of 76% in one isolated specimen. The clinical diagnosis of advanced chronic pancreatitis was refuted by duodenal aspiration, and subsequent laparotomy and biopsy revealed a normal pancreas, the pain being demonstrated by duodenal intubation to be due to biliary dyskinesia.

It should be emphasized, however, that duodenal aspiration will not differentiate between the types of pathological processes affecting the pancreas, but does appear to be, at present, the best means available in individual cases to exclude the possibility of primary pancreatic disease as the cause of symptoms.

In cases characterized by steatorrhœa and wasting the pancreas may be incriminated clinically, and duodenal aspiration may be able to confirm or deny such a possibility. In this series only three patients with definite steatorrhœa and wasting were referred for assessment of pancreatic function; in all three cases normal results were obtained and subsequently two of the patients followed the relapsing course of chronic ileal insufficiency and the other was shown to have Crohn's disease of the ileum.

Three patients were referred for assessment of pancreatic function after an episode of acute hæmorrhagic pancreatitis proven by laparotomy; they were all found to have pancreatic function within normal limits three weeks after their acute episodes.

BILIARY FUNCTION

With the introduction of the secretin test of pancreatic function, attention is again being focused on duodenal aspiration as a test of biliary function, following the observations of Agren and Lagerloef (1937) and others that secretin increases the flow of bile from the liver. If the bile pigment concentration of the duodenal aspirate is followed after the injection of secretin, various types of response are found, succinctly summarized by Howat (1952).

In Type I, the normal response, the bile pigment content of the duodenal aspirate falls markedly, sometimes to zero, in the second and third ten-minute samples after secretin, which cannot be explained on simple dilution of bile by secretin-induced pancreatic juice. This response is interpreted as meaning that the gall-bladder is capable of acting as a reservoir for the increased flow of bile from the liver.

In Type II, after cholecystectomy, or when a " non-functioning " gall-bladder is present, there is no marked fall in bile pigment concentration in the duodenal aspirate after secretin, the increased flow of bile from the liver being discharged continuously into the duodenum.

In Type III, with complete or almost complete biliary obstruction, bile pigments are detected only in small amounts in the duodenal aspirate in both the resting and post-secretin phases.

A Type IV has been described by Dreiling (1950) with a response, intermediate between Type I and Type II, in which, after cholecystectomy, the common bile duct is dilated and

TABLE I

Summary of Illustrative Cases with Findings on Duodenal Intubation

Case No.	Sex.	Age. (Years.)	Clinical Features.	Type of Biliary Response.	Organism Grown from Duodenal Aspirate.	$NaHCO_3$ (Lower Limit of Normal = 80 milli-equivalents)	Amylase (Lower Limit of Normal = 4 units)	Lipase (Lower Limit of Normal = 8 units)	Final Diagnosis.
I	F.	56	Flatulent dyspepsia, boring left upper lumbar pain, and weight loss — six months.	I	—	62	3·4	7·8	Chronic pancreatitis (laparotomy).
II	M.	73	Constant epigastric pain, anorexia, flatulence and weight loss—seven months.	I	—	55	0·1	3·2	Carcinoma of pancreas (laparotomy).
III	F.	32	Attacks of pain in epigastrium and right hypochondrium — six years. No fever or jaundice. Cholecystectomy without relief.	II Biliary dyskinesia; symptoms produced by morphine and relieved by amyl nitrite and atropine.	—	84	5·2	12·4	Biliary dyskinesia (laparotomy).
IV	F.	43	Cirrhosis with features suggesting gall-bladder disease; Graham's test unreliable.	II	—	—	—	—	Chronic cholecystitis (laparotomy).
V	M.	46	Jaundice twelve weeks. Rising serum alkaline phosphatase; negative flocculation tests.	II	*Escherichia coli.*	90	4·8	12·8	Chronic cholecystitis; stone in common duct (laparotomy).
VI	M.	50	Jaundice, pruritus, lumbar pain, weight loss seven weeks.	III	—	35	2·1	1·4	Carcinoma of head of pancreas (laparotomy).
VII	F.	48	Intermittent jaundice with obstructive features—six weeks.	III	—	96	8·4	10·6	Carcinoma of gall-bladder (laparotomy).
VIII	M.	47	Fatty dyspepsia and pain in right hypochondrium for many years—unrelieved by cholecystectomy.	Biliary dyskinesia produced by morphine relieved by amyl nitrite and atropine.	—	—	—	—	Biliary dyskinesia (clinical).
IX	F.	29	Pain suggestive of biliary colic relieved by atropine, not morphine; fever, rigors and mild jaundice.	Biliary dyskinesia as above.	*Escherichia coli.*	90	6·2	11·1	Biliary dyskinesia; chronic cholangitis (clinical).
X	M.	56	Fever, rigors, jaundice.	II	*Escherichia coli* pus cells.	87	6·2	10·6	Chronic cholecystitis and cholangitis (laparotomy).
XI	M.	64	Melæna, jaundice, fever, rigors.	III	Hæmolytic *Staphylococcus aureus* pus cells.	45	1·6	7·0	Chronic pancreatitis; duodenal ulcer (laparotomy).

appears to act as a biliary reservoir, associated with incomplete biliary obstruction, either by residual stone or by stenosis.

Snape *et alii* (1948) have shown that there is a high degree of correlation between the ordinary Graham's test and the secretin test of biliary function both in normal and abnormal conditions of the biliary tract, but suggest that the secretin test has little general application by virtue of its being more cumbersome than oral cholecystography. Dreiling and Lipsay (1951), in a review of three hundred and twenty-seven cases studied by means of the secretin test, again showed the high degree of correlation with Graham's test and pointed out that whereas Graham's test depends on intestinal absorption of the dye, excretion by the liver and concentration in the gall-bladder, the secretin test depends on biliary flow, pancreatic flow, gall-bladder filling capacity, the continence of the biliary sphincters and the degree of obstruction within the bile ducts, suggesting that discrepancies between the results of cholecystography and the secretin test may be explained by the differences in the factors concerned. They point out in addition that the secretin test may be expected to give accurate information in cases in which Graham's test shows no visualization of the gall-bladder, owing to poor intestinal absorption of the dye (diarrhœa, and iodine sensitivity), the presence of marked cirrhosis of the liver, or the presence of jaundice.

More recently Duncan, Howat *et alii* (1950) have produced a pancreozymin preparation which has been used in conjunction with the secretin test to test the capacity of the gall-bladder to contract. It is administered thirty minutes after secretin, and in the normal subject causes the secretin-induced bile, which has been accepted by the gall-bladder, to be discharged into the duodenum. In addition, this pancreozymin preparation appears to act as a specific pancreatic enzyme stimulant.

In this series of cases it was noted that all persons after cholecystectomy gave Type II responses, and those in whom there was nothing to suggest gall-bladder or biliary disease gave Type I responses. In Case IV, with marked cirrhosis of the liver, a reinforced Graham's test failed to reveal a gall-bladder shadow, duodenal intubation and secretin gave a Type II response, suggesting a failure of the reservoir function of the gall-bladder; laparotomy revealed a contracted thick walled gall-bladder without stones, which showed chronic inflammation on section. In Case V, with diminishing painless jaundice, a reinforced Graham's test failed to reveal a gall-bladder shadow, and the interpretation of this finding was in doubt; duodenal intubation and secretin showed a Type II response which suggested biliary disease as the cause of the jaundice. Laparotomy revealed a contracted gall-bladder without stones, and a gall-stone in the lower end of the common bile duct. Case X presented similar features.

The presence of free cholesterol crystals in fresh bile obtained by duodenal aspiration has been mentioned by several authors as evidence of biliary disease. Lichtman (1949) states that such a finding occurs in over 90% of cases of calculous disease of the biliary tract, and goes so far as to say that in competent hands this method is more accurate in diagnosis than cholecystography. Knott (1933), on the other hand, found crystals in only 50% of cases of calculous disease and much less commonly in old standing chronic cholecystitis without stones. In this series microscopic examinations of the biliary sediment were made, and no free cholesterol crystals were seen, even in the two cases in which gall-stones were found in the common bile duct, one in association with a large amount of biliary mud.

It would appear that duodenal intubation and the secretin test may have a place in the diagnosis of biliary tract disease, to supplement oral cholecystography, when Graham's test is contraindicated or when no gall-bladder shadow is seen on radiography and the interpretation is in doubt, namely, with jaundice, cirrhosis of the liver, or when there may have been malabsorption of the dye due to diarrhœa or iodine sensitivity.

Differential Diagnosis of Obstructive Jaundice

Carcinomata of the body and tail of the pancreas do not present initially with jaundice, and the use of the secretin test to assist in the early diagnosis of these conditions is mentioned in the previous section on pancreatic function. Carcinoma of the head of the pancreas, however, commonly presents as obstructive jaundice, and if radical extirpative surgery is contemplated, it may be of help to be certain of such a diagnosis before the surgical attack is commenced, rather than subject the patient to a preliminary diagnostic laparotomy and then to a second operation to excise the tumour. Duodenal intubation can, in most instances, localize accurately the site of the obstructing lesion.

In the section on biliary function it has been shown how the secretin test can show the presence of chronic gall-bladder disease, and partial obstruction of the common bile duct due to stone. In Cases V and X with painless obstructive jaundice the secretin test accurately demonstrated that there was normal pancreatic function, and that there was a disorder of biliary function, after Graham's tests had been held invalid owing to the deep jaundice; laparotomy revealed common duct stones in both instances. In Case VII, with painless obstructive jaundice, in which the clinical diagnosis was one of carcinoma of the head of the pancreas, duodenal intubation and secretin revealed normal pancreatic function, but absence of bile entering the duodenum; a complete obstruction of the common bile duct above the pancreas was implied, and laparotomy revealed carcinoma of the gall-bladder extending to obstruct the junction of the cystic, hepatic and common bile ducts. In Case VI, duodenal intubation demonstrated obstruction to bile flow and a marked diminution in pancreatic exocrine activity and laparotomy revealed a carcinoma of the head of the pancreas, which was resected in one stage. In Case XI, with cholangio-hepatitis superimposed on obstructive jaundice, barium meal showed two active duodenal ulcers which were the cause of the repeated melæna stools. The question arose as to whether inflammation around these ulcers could be the cause of the obstruction; duodenal intubation and secretin demonstrated the obstruction to the flow of bile, but also showed gross diminution in pancreatic function pointing to the pancreas as the prime cause of the obstruction; laparotomy revealed marked subacute and chronic pancreatitis involving the whole gland, the small peptic ulcers being considered as incidental.

Ten patients with obstructive jaundice were submitted to duodenal intubation and the site of obstruction, either primarily pancreatic or biliary, was determined accurately in all cases. This agrees with the findings of Dreiling and Klein (1951), who in a larger group of sixty-three patients found only one whose operative findings had not been predicted accurately; this was a case in which there was a small calculus actually embedded in the wall of the duodenum at the papilla of Vater, obstructing both pancreatic and biliary systems. In Dreiling's experience, other cases with gall-stones at the lower end of the common bile duct did not actually obstruct the flow of pancreatic juice to the duodenum.

It would appear therefore that duodenal intubation with the secretin test can, in most instances, accurately localize the lesions responsible for obstructive jaundice, and this may prove of value prior to remedial surgery.

AFTER CHOLECYSTECTOMY

Unfortunately, it is not rare to find patients who have obtained little benefit from cholecystectomy performed for the relief of digestive symptoms or abdominal pain, even when the gall-bladder has been demonstrated to be the site of organic disease. These cases have been somewhat unhappily labelled instances of the "post-cholecystectomy syndrome", although many types of organic pathology or functional disturbance may be the basis of the symptoms. The situation was well reviewed by Colp (1944); coronary artery diseases, hiatus hernia, peptic ulcer, chronic gastritis, peritoneal adhesions with intermittent obstruction, residual stone in the common bile duct, chronic pancreatitis, hepatic cirrhosis, biliary dyskinesia, "gastric neurosis", are but a few of the factors involved. In any one instance a full assessment of the symptoms and signs is important. When it comes to assessing the function of the biliary tree in these patients, special investigations are limited by the fact that Graham's test is of no value. Duodenal intubation, however, may in some instances give valuable information, without resort to a second laparotomy.

Dreiling (1950) reviewed his findings with duodenal intubation and the secretin test in ninety-eight such patients, in an attempt to find the incidence of chronic pancreatic disease. He found it to be present in only 2% of cases.

In a later review (Dreiling and Lipsay, 1951) in one hundred cases of "the post-cholecystectomy syndrome" the bile pigment responses to secretin were noted. In eighty-three, Type II responses were found, similar in every respect to the response found in patients after cholecystectomy but without symptoms. In a further seventeen patients, nine of whom had jaundice, laparotomy revealed dilatation of the common bile duct due to residual common duct stones or to strictures; of these, ten had a Type IV response indicating a reservoir capacity for bile in the dilated duct, seven however had typical Type II responses. Under these circumstances it would appear that a Type IV response suggests dilatation of the common bile duct, and that laparotomy is indicated, but that a Type II response does not exclude partial common duct obstruction.

In this series, ten cases of "post-cholecystectomy syndrome" were investigated; in

four, duodenal intubation and the secretin test gave no valuable information and in one definite evidence of chronic pancreatitis was found, but here the clinical diagnosis was obvious, in that there was radiological evidence of calcareous degeneration of the pancreas, with *diabetes mellitus* and its vascular complications.

A large literature has accumulated in regard to the symptomatology of biliary dyskinesia and its relationship to " the post-cholecystectomy

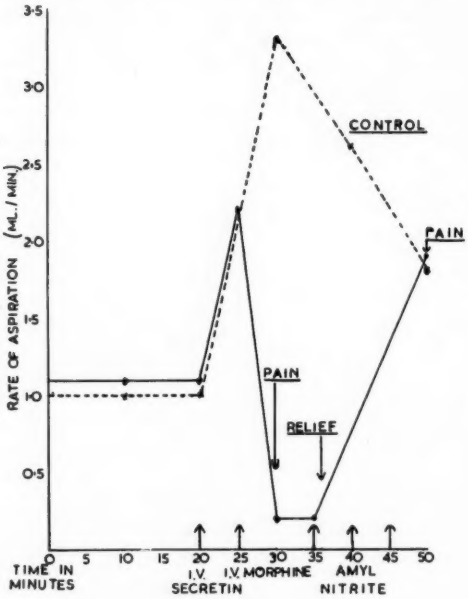

FIGURE II.

Case VIII. The effect of secretin, morphine and amyl nitrite on the volume of duodenal aspirate in a patient with biliary dyskinesia. A control period, in which secretin was used, is graphed for comparison.

syndrome ". The concept in one form of biliary dyskinesia is that there is, in susceptible persons, a neuro-muscular imbalance with spasm of the sphincter of Oddi which may be induced by a variety of causes, local and reflex, by cholangitis, residual calculus, pericholedochal inflammation, traumatic injury to the common bile duct, the exhibition of morphine and in some cases by psychic stimuli. The spasm then results in abnormal pressure relationships within the common duct, with resulting over-distension producing pain similar to biliary colic, nausea and vomiting. Experimental demonstration of this type of biliary dyskinesia in man has only been possible after laparotomy, with a T-tube in the common bile duct, either recording pressure changes in the biliary system by a manometer, or watching serial radiographs of dye locally introduced into the biliary tree, after various stimulants. More recently Royer *et alii* (1950) have studied this syndrome of biliary dyskinesia by means of peritoneoscopic cholangiography, obviating the necessity of laparotomy and the T-tube, but necessitating the presence of the gall-bladder into which the radio-opaque dye is injected through the peritoneoscope.

In this small group of ten cases of " the post-cholecystectomy syndrome ", five were due to this type of biliary dyskinesia, in which the intravenous injection of morphine (one quarter of a grain) caused spasm of the sphincter of Oddi with sudden onset of the typical severe pain to which the patients were subject. By duodenal intubation it was found possible to demonstrate the presence of the sphincter spasm.

Figure II illustrates the situation in Case VIII. An ordinary control secretin test was performed with collection and measurement of the duodenal aspirate in two preliminary ten-minute samples, and three ten-minute samples after the injection of the appropriate dose of secretin. Fasting enzyme estimations and the maximum bicarbonate concentration on the aspirate showed no evidence of pancreatic disease, and the bile pigments showed a typical post-cholecystectomy Type II response. The patient was then left at rest with the tube *in situ* for one hour. At the conclusion of this period, another two ten-minute samples of duodenal contents were aspirated which were almost identical in volume to those in the control period. An equivalent injection of secretin was again given, followed later by morphine sulphate, one-quarter of a grain given intravenously. Three minutes later the patient complained of excruciating pain in the epigastrium and right hypochondrium, exactly similar to the severe attacks of spontaneous pain. At this time it was noted that the volume of duodenal aspirate had fallen almost to zero. Amyl nitrite was given by inhalation, pain was relieved some two minutes later, and the duodenal aspirate commenced to increase in volume. Amyl nitrite was given at five minute intervals until thirty minutes after the injection of secretin, when the volume of aspirate was comparable to that in the control period. At this time the duodenal tube was removed, pain recurred and was finally alleviated by the exhibition of atropine sulphate, one-fiftieth of a grain, intravenously.

Four other cases gave identical results, with almost complete cessation of flow of secretin-induced duodenal aspirate after the intravenous

injection of morphine with occurrence of pain identical in all respects to their spontaneous episodes, and relieved temporarily by amyl nitrite inhalation, or permanently by a large intravenous dose of atropine. One of these cases (Case IX) was associated with cholangitis, and in another (Case III) a subsequent laparotomy was performed and no abnormality could be detected either in the pancreas or in the biliary system after thorough exploration. Colp (1944) asserts that the presence of biliary dyskinesia does not exclude the possibility of a residual common duct stone.

It is suggested, therefore, that duodenal intubation and a secretin test may give valuable information in some cases of " the post-cholecystectomy syndrome ". In addition it is suggested that such a test could be followed by a morphine sensitivity experiment similar to that described, to demonstrate whether a biliary dyskinesia exists with resulting spasm of the sphincter of Oddi, such demonstration being impossible even at laparotomy except with the insertion of a T-tube and subsequent manometric or cholangiographic techniques.

BILIARY INFECTION

Several papers in the past have been written on the use of duodenal intubation in isolating organisms responsible for biliary infection. Many elaborate precautions have been suggested to ensure the bacteriological sterility of the aspirate, but a review by Nauss *et alii* (1931) suggested that the methods in which a single lumen tube was used were unreliable.

We have developed a method which is simple and, although not aiming to be bacteriologically sterile, has been found of value. Prior to intubation, the tube is rinsed with " Zephiran " (1 in 200) and fully immersed in a solution of " Zephiran " (1 in 200) for one hour and is then thoroughly rinsed twice with running tap water. It is then passed in the usual way. The connexion tubing to the receiving vessel is treated in a similar manner. When the tube tip is in the appropriate place and the proximal balloon is inflated, suction is applied and the first ten-minute sample is discarded as it appears to contain most of the contaminants introduced with the tube from the patient's mouth. A second specimen is then collected into a sterile container and submitted for bacteriological examination. In five controls in which there was no reason to suspect biliary infection, no growth was obtained on culture. In the others one organism was predominant on culture and its *in vitro* sensitivity has been tested.

In recent years there has been a widespread introduction of powerful antibiotics which act efficiently in the biliary system, by virtue of their concentration in the liver and excretion into the bile ; however, it has been noted by several observers that *pari passu*, there has been, in hospital populations, an increasing number of organisms resistant to such antibiotics, so that in this hospital at least, in the Fairfax Institute of Pathology, it is customary to perform *in vitro* antibiotic sensitivity tests on most bacteriological material submitted.

Case X posed the problem of a cholangiohepatitis which had received in the previous three months several antibiotics, without response. The surgeon was unwilling to perform laparotomy until fever and toxæmia had abated, with diminution in jaundice and improvement in liver function. The appropriate antibiotic was needed and duodenal intubation was requested to aspirate a sample of bile. As a result, an organism, *Escherichia coli*, was cultured and found to be insensitive *in vitro* to the aureomycin which was being exhibited, but sensitive to streptomycin. Streptomycin was given with rapid resolution of fever and jaundice and improvement in liver function ; the subsequent cholecystectomy and removal of stones from the common bile duct were not followed by liver failure.

In Case XI with a similar picture of swinging fever, and obstructive jaundice, proved by duodenal intubation to be of pancreatic origin, a scanty amount of bile stained fluid was aspirated, which on culture revealed hæmolytic *Staphylococcus aureus* (coagulase positive), which was found *in vitro* to be insensitive to penicillin, streptomycin, aureomycin and terramycin, but sensitive to "Chloromycetin". "Chloromycetin" was given, the fever subsided and the patient's general condition improved somewhat ; at laparotomy a specimen of bile taken from the common bile duct was found to contain sterile pus.

In Case IX, in addition to the biliary dyskinesia, there had been a history of fever with jaundice following cholecystectomy, with residual malaise and abnormal results to liver flocculation tests, duodenal drainage revealed *E. coli* on culture which was insensitive *in vitro* to terramycin, but sensitive to aureomycin, " Chloromycetin " and streptomycin. A course of aureomycin was given with marked symptomatic improvement both as regards malaise and the pain of the biliary dyskinesia, associated with a return to normal of the liver function test results.

Two other cases were seen, with a provisional diagnosis of acute cholecystitis, in which young women had episodes of fever and slight jaundice; these episodes were of short duration, but there was residual malaise and liver function tests gave abnormal results; Graham's test gave normal results, but duodenal drainage showed *E. coli* on culture. A diagnosis of subacute cholangitis was made in each instance and both patients responded well to aureomycin, both as regards symptoms and liver function tests.

It is to be noted that *E. coli* is not a normal inhabitant of the biliary system nor of the duodenum (Lichtman, 1949) except in the presence of achlorhydria (Ricen *et alii*, 1928).

These findings show that duodenal aspiration may be of value in isolating a pathogenic organism from the biliary tract, and in permitting drug sensitivities to be determined.

SUMMARY

1. The aim of this paper has been to show that by duodenal aspiration much information can be gained in relation to biliary and pancreatic disorders, which cannot otherwise be revealed except by laparotomy and in the case of certain types of biliary dyskinesia not even then.

2. Duodenal intubation has been found to be an easy procedure on fasting patients under hospital conditions.

3. No satisfactory screening test for chronic pancreatic disease has yet been elaborated. However, in certain selected cases the combination of duodenal aspiration with the secretin test will give valuable information as to whether the pancreas is, or is not, involved as the seat of primary disease in accounting for abdominal pain of obscure origin, or wasting syndromes with steatorrhœa.

4. The use of secretin with duodenal aspiration may serve as a test for biliary function, and it correlates well with Graham's test. It can, however, be used with success in the diagnosis of chronic gall-bladder disease where Graham's test is unlikely to give satisfactory results, namely in the presence of jaundice, with advanced cirrhosis of the liver, iodine sensitivity or small bowel malabsorption of the dye.

5. Duodenal intubation can often localize the lesion in cases of obstructive jaundice.

6. In cases of recurrent pain after cholecystectomy, duodenal intubation and the secretin test show that chronic pancreatitis is an uncommon cause; the secretin test can assist in revealing the presence of residual stone in the common bile duct with partial obstruction.

7. Duodenal intubation with the use of secretin followed by morphine can show that a "post-cholecystectomy syndrome" is in some cases due to biliary dyskinesia, with sensitivity of the sphincter of Oddi to morphine, which cannot be otherwise demonstrated short of laparotomy and bile duct manometry.

8. Duodenal aspiration can, without elaborate bacteriological sterility, be of considerable use in the isolation of organisms responsible for biliary infections; in these days of antibiotic resistance it may be necessary to test such organisms for their *in vitro* sensitivity to permit the rapid control of a cholangio-hepatitis prior to remedial surgery within the biliary system.

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APPENDIX

Synopsis of Case Histories

CASE I.—E.B., a spinster, aged fifty-six years, presented with an illness of six months' duration, characterized by epigastric distension after meals, flatulence, continuous but ill-defined epigastric aching pain, and boring back pain felt to the left of the mid-line in the upper lumbar region, associated with anorexia and the loss of 4·5 kilograms in weight. No relief had been obtained by alkaline powders or with local heat. There were no abnormal physical signs. No abnormality had been discovered after several special investigations, including two barium meals, barium enema, cholecystogram, excretion pyelogram, microscopic examinations of the urine, test meal, and radiographic studies of the vertebral column. She had been seen by several practitioners and confidently labelled as "non-organic". A month's rest in the country was prescribed without improvement. On duodenal intubation, with the secretin test, a Type I biliary response was obtained, the maximum bicarbonate response being 62 milliequivalents per litre, fasting lipase being 7·8 units, and amylase 3·4 units, indicating a deficiency in pancreatic function. Laparotomy revealed a nodular and indurated pancreas showing chronic pancreatitis. A left infra-diaphragmatic splanchnicectomy was followed by marked, although not complete, relief of symptoms.

CASE II.—J.W., a male, aged seventy-three years, presented initially with essential hypertension and a myocardial infarct. For the seven succeeding months he complained of a dull aching pain in the epigastrium, day and night, unrelated to food, not relieved by alkalis, but associated with marked flatulence, anorexia and constipation. Over this period there was loss of 10 kilograms in weight. There had been no dysphagia or bleeding. Physical examination revealed no definite abnormality except hypertension. Special investigations showed a histamine-fast achlorhydria; a small sliding type of hiatus hernia and a cascade type of stomach were seen on barium meal examination. It was considered not impossible that these findings could account for the illness. Duodenal intubation and secretin revealed a Type I biliary response; the maximum bicarbonate response was 55 milliequivalents per litre, with fasting lipase 3·2 units and amylase 0·1 unit, indicating a marked deficiency in pancreatic function. A subsequent laparotomy revealed a large inoperable carcinoma of the body of the pancreas.

CASE III.—I.S., a female, aged thirty-two years, had on several occasions been admitted to the psychiatric department of the hospital with the diagnosis of hysteria. In 1945, she was admitted with a six months' history of right upper quadrant pain and vomiting, with severe attacks suggestive of biliary colic, but without fever or jaundice. A reinforced Graham's test had not shown a gall-bladder shadow and at laparotomy chronic cholecystitis and cholelithiasis were found. Cholecystectomy was performed without exploration of the common bile duct. In 1946, while pregnant, the patient developed *diabetes mellitus* and was delivered by Cæsarean section. The diabetes subsequently had been difficult to control; she had been admitted to hospital on several subsequent occasions with hypoglycæmic attacks or incipient diabetic coma, but even in hospital the diabetes had been difficult to stabilize. Over the period up to September 1951, the patient had been subject almost monthly to attacks of spontaneous pain, sometimes moderate, sometimes severe, sharp, felt in the epigastrium, right hypochondrium, lasting one to two hours, similar to biliary colic, but without a definite colicky element, without jaundice, fever or disturbance of general health. On examination no significant abnormality could be detected. Special investigations including barium meal examination revealed no abnormalities, except that one isolated specimen of

stool showed total fat to be 76% of the dried weight of the fæces. The diagnosis of chronic relapsing pancreatitis was made in view of the history of pain, the presence of *diabetes mellitus* and steatorrhœa. Duodenal intubation and the use of secretin showed a Type II biliary response, the maximum bicarbonate response was 84 milliequivalents per litre, fasting lipase 12·4 units, and amylase 5·2 units, indicating pancreatic function within normal limits. An injection of morphine sulphate, one-quarter of a grain, was followed by an attack of severe pain similar to that of which the patient complained, associated with almost complete cessation of flow of the duodenal aspirate. The pain was relieved temporarily by the inhalation of amyl nitrite, with temporary reestablishment of the flow of the aspirate; pain was relieved permanently by intravenous atropine sulphate, one-fiftieth grain. The diagnosis of biliary dyskinesia was made and the patient discharged. She was readmitted later under the care of a surgeon, who was unaware of the previous findings, with the provisional diagnosis of stone in the common bile duct; laparotomy and exploration of the biliary system showed no abnormality, no residual calculus, the pancreas being normal to palpation and on biopsy.

CASE IV.—M.T., a female, aged forty-three years, was admitted to hospital with an eighteen months' story of repeated attacks of nausea, vomiting, diarrhœa and abdominal discomfort and generalized itching, lasting three to four hours. On examination there were marked cutaneous pigmentation, slight icterus, xanthelasmata, and spider nævi. The liver was enlarged 10 centimetres below the right costal margin in the mid-clavicular line without ascites, splenomegaly or engorged abdominal veins. Liver function tests showed bromsulphalein retention 30%, serum bilirubin content 3·5 milligrammes *per centum*, thymol flocculation "++++", serum alkaline phosphatase 34 King units. The possibility of an obstructive factor producing a biliary cirrhosis was considered. With a reinforced dose, no shadow of the gall-bladder was seen on cholecystography (oral administration); the interpretation of this finding was in doubt in view of the gross disturbance of liver function. Duodenal intubation and secretin revealed normal pancreatic function, but a typical Type II biliary response, suggesting a failure in the reservoir function of the gall-bladder. Laparotomy revealed portal cirrhosis of the liver (biopsy) and a small contracted thick walled gall-bladder without calculi which was resected, showing chronic cholecystitis on section.

CASE V.—J.L., a male, aged forty-six years, presented with jaundice of seven weeks' duration. Its onset had been sudden, without pain, but preceded by anorexia and malaise, which had subsided after the appearance of jaundice. Stools had been clay coloured only initially. The liver was enlarged five centimetres below the right costal margin. A clinical diagnosis of slowly resolving hepatitis was not supported by the liver function tests, serum bilirubin content 14·5 milligrammes *per centum*, thymol flocculation "negative", serum alkaline phosphatase 24 King units. Over the next month there were no symptoms, and jaundice gradually diminished but did not disappear, thymol flocculation remained "negative" but the serum alkaline phosphatase level rose to 50 King units. A reinforced cholecystogram failed to outline the gall-bladder. In view of the presence of jaundice, the interpretation of the result of this test was difficult. Duodenal intubation and secretin showed a Type II biliary response, the maximum bicarbonate level was 90 milliequivalents per litre, fasting lipase 12·8 units, amylase 4·8 units. This suggested normal pancreatic function, but an abnormality in the biliary system. Microscopic examination of the aspirate showed no cholesterol crystals, but on culture *Escherichia coli* sensitive to antibiotics other than aureomycin was revealed. Laparotomy showed a normal pancreas, a small thick-walled gall-bladder and a calculus in the lower end of the common bile duct without gross dilatation above it.

CASE VI.—J.O., a male, aged fifty years, presented with a history of seven weeks' jaundice, generalized pruritus, aching in the lumbar region of the back, clay coloured stools and the loss of 10 kilograms in weight. On examination the liver was enlarged two centimetres below the right costal margin. The clinical diagnosis of carcinoma of the head of the pancreas was confirmed by duodenal intubation, when only ten millilitres of slightly bile-stained fluid were obtained in the fasting specimen with lipase 1·4 units, amylase 2·1 units. After the exhibition of secretin there was no increase in bile flow (Type III response), only 16 millilitres of fluid being aspirated in the succeeding thirty minutes with a maximum bicarbonate level of 35 milliequivalents per litre—indicating obstruction to both biliary and pancreatic flow. At laparotomy, a carcinoma of the head of the pancreas was found, and a radical excision was performed in one stage.

CASE VII.—A.S., a female, aged forty-eight years, presented with a history of six weeks' painless jaundice which had waxed and waned, the stools being intermittently clay coloured, with the loss of two kilograms in weight. The liver was palpable two centimetres below the right costal margin. A provisional diagnosis of carcinoma of the papilla of Vater was made; on duodenal intubation with secretin, no bile was aspirated (a Type III response), fasting lipase content was 10·6 units, and amylase 8·4 units, the maximum bicarbonate level was 96 milliequivalents per litre, suggesting that there was complete biliary obstruction, without abnormality of the pancreatic system. A centrifuged deposit of the aspirated material showed epithelial cells but no carcinoma cells. Laparotomy revealed a carcinoma of the gall-bladder extending to involve the junction of the cystic, hepatic and common bile ducts.

CASE VIII.—R.M., a female, aged forty-seven years, presented initially in 1944, with an attack of biliary colic preceded by many years' fatty dyspepsia. The gall-bladder containing three calculi was removed after the common duct had been explored. Subsequently the fatty dyspepsia had persisted, with postprandial epigastric pain poorly relieved by alkalis. In addition at approximately four-monthly intervals there had been episodes of severe non-colicky pain felt in the epigastrium, right hypochondrium and upper lumbar region of the back associated with prostration and vomiting, lasting two to three hours, relieved by atropine but never by morphine. There had never been jaundice. The patient had been treated for duodenal ulcer which had not been revealed on radiological examinations. No abnormality was detected on physical examination. Special investigations showed no abnormalities. Duodenal intubation and secretin followed by morphine (Figure II) induced the typical pain, associated with a marked diminution in flow of the duodenal aspirate, reversed temporarily by amyl nitrite and permanently by atropine.

CASE IX.—B.C., a female, aged twenty-nine years, presented with a three years' history of attacks of pain similar to biliary colic, associated with vomiting,

fever and rigors without jaundice. The pain was unrelieved by morphine but alleviated by atropine. In addition she complained of a continuous nagging ache in the right hypochondrium often aggravated by intake of food. She was admitted to hospital following a similar severe attack of pain and fever, this time with slight jaundice which abated rapidly. Physical examination showed no definite abnormality; repeated Graham's tests gave normal findings. A laparotomy and exploration of the bile ducts revealed no abnormality and a cholecystectomy was performed. After discharge the patient had continuous malaise and a further episode of colicky pain and fever. On duodenal intubation with secretin, there was a Type II biliary response, the fasting amylase content was 6·2 units and lipase 11·1 units, the maximum bicarbonate response being 90 milliequivalents per litre, suggesting normal pancreatic function. After the exhibition of morphine the characteristic severe pain was induced with marked diminution in the flow of aspirate, reversed by atropine given intravenously, suggesting biliary dyskinesia with sphincter of Oddi spasm. Liver function tests revealed thymol flocculation "+++" and a serum bilirubin content of 1·0 milligramme *per centum*; bile, on culture, revealed *E. coli* sensitive *in vitro* to aureomycin. After a course of aureomycin, symptoms disappeared and the results of liver function tests returned to normal values.

CASE X.—W.N., a male, aged fifty-six years, had one episode of biliary colic in 1947, with a "non-filling gall-bladder" on cholecystography and was treated conservatively. His present illness had been of six weeks' duration, with episodes of fever, rigors and sweating, but without jaundice or localizing features. These episodes had been treated in turn with aureomycin, "Chloromycetin" and terramycin, with immediate relief but with relapse within one week of the cessation of antibiotic therapy. He was admitted to hospital with fever and jaundice of one week's duration, with normally coloured stools, having lost 65 kilograms in weight. On examination the patient was extremely ill, with an enlarged tender liver. He was considered to have Charcot's intermittent fever with cholangio-hepatitis, and was treated with aureomycin. Over the first week the patient's condition declined with a hectic fever, daily rigors, and increasing jaundice. Duodenal intubation and secretin showed a Type II biliary response, a fasting lipase content of 10·6 units, and amylase 6·2 units, and a maximum bicarbonate response of 87 milliequivalents per litre, indicating biliary rather than pancreatic disease. Pus cells but no cholesterol crystals were seen on microscopic examination of the aspirated bile, which on culture yielded *E. coli* sensitive *in vitro* to streptomycin, but insensitive to aureomycin. Streptomycin was administered with cessation of the fever within twenty-four hours; jaundice abated, liver function and the patient's general condition improved, and laparotomy revealed a thick contracted gall-bladder containing two stones and several small stones and biliary mud in the common bile duct. Cholecystectomy and drainage of the common bile duct were performed, without post-operative jaundice or liver failure.

CASE XI.—W.H., a male, aged sixty-four years, was admitted to hospital for resection of the sigmoid colon for diverticulitis and stenosis; he had suffered from a proven duodenal ulcer for many years. Prior to admission he had several melæna stools and had noticed jaundice, fever and rigors for some five days. On examination there was a large tender liver. Melæna continued in hospital and necessitated several blood transfusions, a barium meal examination revealing two ulcers in the duodenal cap. Jaundice increased in depth and was associated with a hectic fever and daily rigors. Liver function tests revealed a serum bilirubin content of 19 milligrammes *per centum*, thymol flocculation "++++" and serum alkaline phosphatase 66 King units. The patient's condition deteriorated despite the exhibition of sulphonamides, penicillin, streptomycin and aureomycin. Duodenal intubation and secretin revealed fresh blood in the duodenum and only a small amount of bile (Type III response), a fasting lipase content of 7·0 units, amylase 1·6 units with a maximum bicarbonate response of 45 milliequivalents per litre, indicating that the pancreas was the site of the primary obstructive disorder. Microscopic examination of the bile showed no cholesterol crystals, but numerous pus cells, which on culture revealed hæmolytic *Staphylococcus aureus* (coagulase-positive) insensitive *in vitro* to streptomycin, penicillin, aureomycin and terramycin, but sensitive to "Chloromycetin". "Chloromycetin" was exhibited with cessation of the fever and improvement in the patient's general condition and liver function. Laparotomy revealed two small duodenal ulcers, subacute and chronic pancreatitis involving the whole gland with obstruction to the common bile duct from which pus was aspirated, this being sterile on cultivation; a cholecyst-enterostomy was performed.

COMPARATIVE STUDIES IN VECTOR AND LINEAR ELECTROCARDIOGRAPHY[1]

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Considerable disagreement has been expressed by numerous writers on the relative values of the electrocardiograms recorded from various leads. The significance of variations from the normal in these leads and the theoretical validity of the various leads themselves have also been called into question (Gillman, 1951; East and Oram, 1952; Oram, 1949; Nahum and Hoff, 1948).

In this paper it will be shown that the doubts cast upon validity and value can be upheld under certain circumstances without prejudicing the fundamental hypothesis of the Einthoven Theory.

It will be shown that one, at least, of the methods in use for recording the electrical activity of the heart is free from an important source of unreliability common to many other techniques.

The relative reliability of various spatial and planar vector loops, which are obtainable, will be assessed.

For this purpose it is necessary to define reliability and accuracy. Reliability is assessed by comparing magnitudes of the observed electrocardiogram and the electrocardiogram calculated from the projection of the vector loops on the particular lead. The ratio of observed to calculated magnitudes is used. This comparison assumes that the vector loop is a universal, reliable representation of the heart's electrical activity. Under some conditions the vectorcardiogram is universally reliable, as will be shown.

As far as accuracy is concerned, once the anomalies due to unreliability are removed, the accuracy of representation in any lead system depends only upon the suitability of the Einthoven theory in practice, and as such will not be discussed here.

It is frequently claimed that of the many available leads, some are based upon different plane systems from others (Wolferth *et alii*, 1941), and hence that the vectorcardiograms synthesized from leads in one system cannot represent those of another (Hill, 1938; Rasmussen and Box, 1951; Haney *et alii*, 1933; Grant, 1950*a*, *b*). If so, the vectorcardiogram cannot give a true representation of all the body leads in use. This will be demonstrated in the paper, but it will be shown that the discrepancy lies neither in the vectorcardiogram nor in the curiously variable characteristics of individual hearts, but simply in the physical inhomogeneity of the body and in the use of single unipolar or bipolar leads. In other words, the anomalies in some leads, viewed in the light of a "correctly synthesized" vector loop, are not a feature of a given heart *per se*, or inherent errors in the leads, but the result of the method of developing an electrical field within the body (Sayers, 1952). These anomalies may be considered as "errors", defined as follows:

For a potential-position electrical field distribution of the polar coordinate form

$$V=\frac{2M\cos\theta}{kr^2}$$

where V is the potential; r, θ are the polar coordinates of point P, and M is the dipole moment.

The apparent uncertainty of "error" fraction in V is $\frac{\delta V}{V}$, due to a variation $\delta\theta$ in θ, which is the result of slight inhomogeneity of the electrical medium.

The error fraction has been calculated for large θ_P (Sayers, 1952) to be

$$\frac{\delta V}{V}=\tan\theta_P\,.\,\delta\theta$$

where θ_P is the angle between electrical axis and radius vector of point P.

For small values of θ_P this relationship is slightly modified. Hence the range of uncertainty is from $0\rightarrow100\%$ as θ moves from $0\rightarrow90°$.

[1] Received for publication on August 14, 1952.

INITIAL STATEMENT OF THE THEORY

This contention being held, a theory of unreliability has been developed.

It is believed that the manifest electrical activity of the heart may be described accurately as an electrical dipole whose radius vector traces out a spatial loop according to a fixed individual characteristic. Wide variation has been shown in the shape and size of the vector loop from one individual to another.

It is immaterial what nature of field structure is assumed for the body, since a cosine term must appear in all applicable potential-position distributions. There are undoubtedly certain inhomogeneities present in the electrical conducting medium of the body; it has been shown (Sayers, 1952) that there will be an "error" between the actual electrocardiogram in any lead and that calculated for that lead from the vectorcardiogram. The "error" depends on the angle between the loop and the lead. If this angle has approached 90° for any lead used for obtaining the vector loop then the vector loop so obtained will be *per se* largely erroneous unless certain lead structures are used (see below). In other words, any correlation between calculated and observed electrocardiograms under these conditions will be fictitious or misleading. However, let us consider that the vectorcardiogram has been correctly obtained. Then, according to the angle between the lead and the loop, there will be a calculable "error" between observed and calculated electrocardiograms.

If the evidence supports the existence of a fixed "error" angle law as discussed by Sayers (1952), then we may state as follows:

1. The "errors" in leads at or near right angles to the loop will in nowise be characteristic of specific cardiac abnormalities, for they are a feature of the fundamental manner of establishing the heart's electrical field. Hence, under these conditions the electrocardiogram peculiarities occurring at lead-loop angles approaching 90° will have no significance in diagnosis.

2. The vectorcardiogram cannot be questioned simply because of such poor correlation; in other words, if the vectorcardiogram can be shown to have been obtained according to correct angle relationships, then the vectorcardiogram is a more significant representation of the heart's electrical activity than those electrocardiogram leads for which $\theta \rightarrow 90°$. Under this angle condition these electrocardiogram leads can have no significance and may therefore be misleading. If the correct vectorcardiogram loop in one planar projection happens to be "thin" or "narrow", then for leads in this plane at or near right angles to the loop direction, an "error" will be present uniformly over the whole electrocardiogram complex. However, if it can be shown that the vectorcardiogram is only at right angles to the lead over part of the electrical cycle, then evidently the "error" will appear only over such portions of the cycle. Thus it is not surprising to find an apparently erroneous *QRS* complex occurring together with an apparently correct *T* wave, when the *QRS* and *T* loops are at different angles. It has been shown (Grant, 1950*a*) that there is normally an angle of 0° to 50° between the spatial *QRS* and *T* loops. Thus there is always present a fixed known "error" *versus* angle relationship for the electrocardiograms recorded from leads in the electrical field of the body. "Error" describes poor correlation between observed electrocardiograms and those calculated from the vector loop, where the vector loop has been correctly obtained, and hence between observed electrocardiograms and those calculated from electrocardiograms or vectorcardiograms which are independent of the location of leads.

3. The correctness of the vector loop can always be determined thus: if good correlation can be shown between calculated and observed electrocardiograms in leads taken at small angles to the apparent loop axis, correction being allowed for chance correlation, then that vector loop may be assumed correct. If this correlation is not satisfactory, then rotation and/or translation of the leads must be resorted to until such a satisfactory agreement has been obtained. The minimum "error" will in general be obtained in synthesizing a planar loop when the angle of the loop to both leads is 45°. If the angle to one decreases, improving the exactness, the angle to the other increases, reducing the exactness. Hence it is obvious that a vector loop cannot always be an exact representation of the heart's electrical activity because of internal factors which have some weight when $\theta = 45°$. This will not necessarily be the case with any specific electrocardiogram lead, but without a satisfactory vector loop for reference erroneous leads at or near 90° cannot be recognized. Furthermore, long narrow loops will always give best correlations, because θ does not then vary over a wide range during one complex. If the "error"-angle law can be shown to be obeyed with good agreement in practice, then apparently characteristic electrical activities of the heart must be greatly

more exact than the electrocardiograms normally permit us to measure.

In the investigation of the electrocardiogram, therefore, the only significant studies are those pursued with constant references to the best obtainable vector loop.

Experimental Verification

There is considerable evidence in the literature which agrees with, and apparently cannot be explained except by the present theory. This

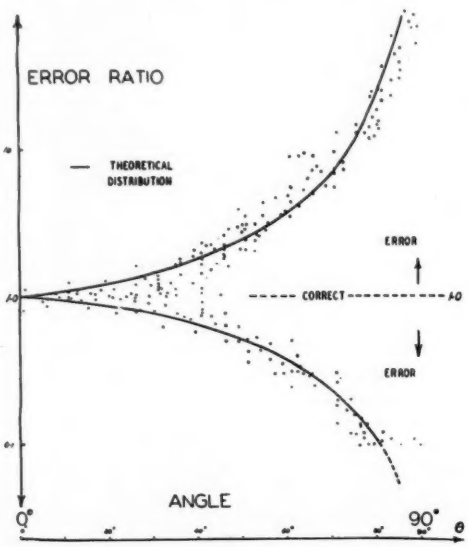


Figure I.
Error-angle distribution curve. The dotted points are observed values of the function.

has been discussed by Sayers (1952); one example will be quoted here.

Duchosal and Sulzer (1949) took loops with rectangular leads in the horizontal planes through the body, and then repeated these measurements with lead systems rotated through 45°. They found in one experiment, without apparently realizing the significance of the investigation, that the two loops on any one plane were not entirely comparable, but became more so as successive planes down the body were used for measurement. They were able to show good agreement in this case from only one plane. There the two vector loops gave good agreement, hence demonstrating that the angle between that plane and the electrical vector was close to zero.

Method

In the present series a set of 40 cases was chosen for convenience from normal and hypertensive individuals, often with abnormal traces. Reproductions from results of only nine of these have been included here.

The horizontal, frontal and sagittal loops were synthesized on a cathode ray tube vectorcardiograph, according to the method of Duchosal and Sulzer (1949). The two papers quoted have demonstrated the general validity of the vector method of representation of the

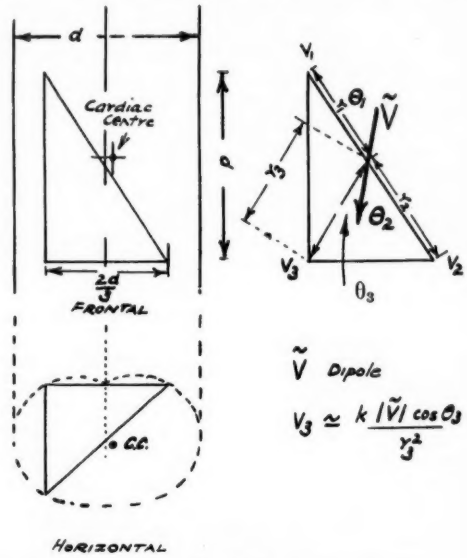


Figure II.
Geometrical properties of the Duchosal-Sulzer electrode system.

cardiac electrical activity. Horizontal loop studies have been presented here because of the particular significance of the present theory to the use of the unipolar chest leads, but it is to be emphasized that the effect described has been clearly demonstrated for all leads and all planar representations. In order to illustrate this, one set of frontal leads (*VR* and *VL*) has been also shown.

The observed electrocardiograms prepared with various leads, and those calculated from the vector loop, have been compared, and the results are demonstrated in Figures III to XI. In all cases a specific scaling factor common to the observed waves in that case and another common to the calculated wave have been employed merely for convenience.

Correction for lead point distances from the heart has also been made, and the direction of

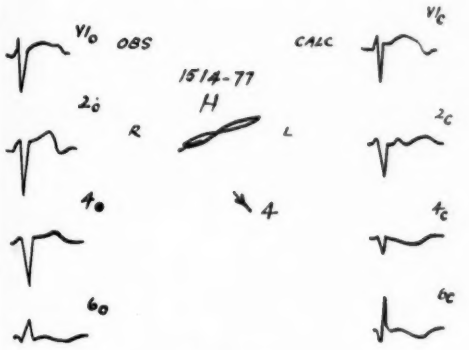


Figure III.

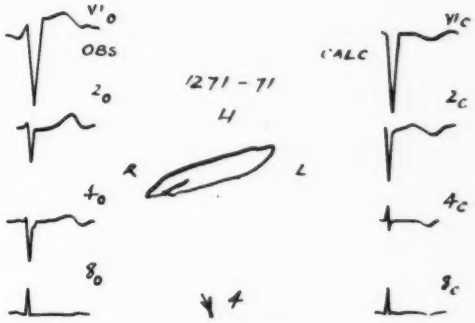


Figure IV.

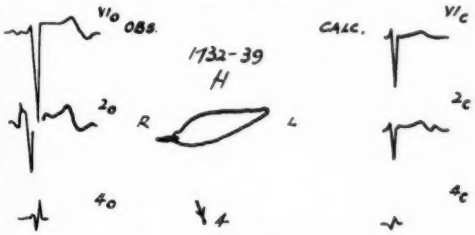


Figure V.

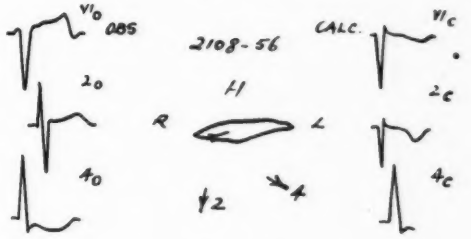
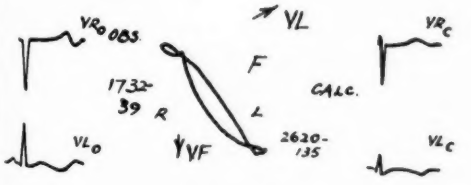


Figure VI.



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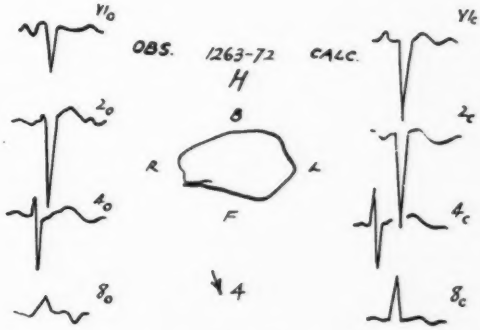

Figure IX.

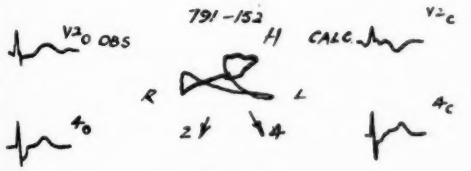

Figure VIII.

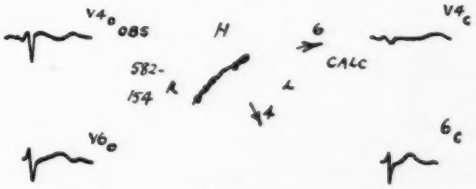

Figure XI.

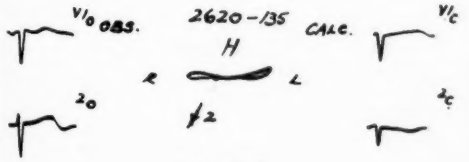

Figure X.

FIGURES III-XI.

Typical observed linear electrocardiograms compared with those calculated from the vectorcardiograms.

Note.—Leads V_1, V_2 *et cetera* are the unipolar chest leads referred to Wilson terminal. VR, VL, VF are similarly unipolar limb leads. H represents a horizontal vector loop, F a frontal loop; R, L, F, B, around the vector loop, indicate right, left, front, back. Subscripts "O" and "C" indicate observed and calculated electrocardiograms.

each lead was calculated from the mid-point of the interventricular septum (Duchosal and Sulzer, 1949), determined in each case by radiological and sonic measurements.

Results

It was evident from the observations that the relative sizes of the observed and calculated QRS and T waves varied from lead to lead in each case. In other words, the ratios

$$\frac{QRS \text{ obs.}}{QRS \text{ calc.}} \text{ and } \frac{T \text{ obs.}}{T \text{ calc.}}$$

in any and each case, varied according to the lead under study. The ratios varied with the angle between the direction of the major axis of the QRS or T loop and that of the lead. Most leads reported here were unipolars, but the effect is found in bipolars also.

As the angle θ increased from zero towards 90°, the ratios varied from their zero angle value, becoming either very large or very small. This was found in all cases. However, in assessing the ratio-angle relationship, irregularities were found, but only in the presence of a wide angle vector loop. Furthermore, in these cases, the shape of the observed QRS and T waves made it difficult to compute the ratio in the presence of complex waves, and hence the following modification was adopted.

First, it was assumed that the sign of the wave should be ignored in biphasic waves, but that the ratio of positive to negative segments was important. This was done because of the difficulty in providing a rational error computation on two waves in which such a state obtained.

Second, it was decided to compare the magnitudes of observed and calculated waves at specific phases of the loop or cycle. This then would permit an estimate of the QRS and T ratios for a specific measurable direction of the vector component. Since it was found that on the available apparatus the linear lead waves could be measured to approximately one-fiftieth of the total period, the waves were measured at 25 equal intervals of phase and compared with the appropriate angles also measured at simultaneous phases of the loop.

It was then found that the comparison between calculated and observed waves from leads at small angles ($\pm 15°$) to the instantaneous vector direction, was good in all cases. Thus the magnitudes of the ratios were referred in magnitude to the weighted mean of these small angle ratios. Since all cases showed an accurately calculable mean ratio for each case in small angle leads, this was justified in practice.

This ratio of $\frac{QRS \text{ obs.}}{QRS \text{calc.}}$ to the mean at small angles was calculated and plotted against angle θ on a semi-logarithmic graphical scale. Values of the ratio below 0·1 were not plotted because of the difficulty of accurate measurement at small values, but in a few cases in which accurate estimation was possible the progression of points fitted the other observations satisfactorily (Figure I).

In observing this graph two points should be noted: (i) The ordinate actually provides an estimate of error, this being zero error at unit ordinate. (ii) Since errors may be due to the observed waves being too small, or too large, the curve must be expected to contain two branches.

Another observation is that in situations in which errors occur, these errors fall into one of two clear patterns: (i) There may be no qualitative or quantitative agreement between observed and calculated waves. This is found slightly less frequently than the second pattern. (ii) There may be some qualitative but inadequate quantitative agreement.

In general, it has been found that the closer a given lead approaches 90° to the loop axis, the more frequently the first pattern appears.

Discussion

It has been demonstrated theoretically (Sayers, 1952) that there is an error-angle relationship associated with the establishment of a field of an electrical dipole in the human body. This error is the direct result of inhomogeneities present in the body as an electrical conducting medium.

The present study demonstrates that these errors are actually found in practice. The ample proof of this effect presented in these pages is suggestive of several significant points:

1. The distribution of the electric field in the body seems to obey a law of the dipole type, and in view of the good correlation between observed and calculated leads under certain conditions, it is apparent that the vector method of representation is suitable.

2. The fact that errors occur according to a tight distribution, and in a manner such as is expected on the present theory, seems to add further weight to the use of the vectorcardiogram.

3. Such a relatively tight error distribution suggests not only that the nature of the source generators of the field is remarkably uniform from case to case, but that the significant and

controlling inhomogeneities are remarkably constant from case to case. There is, however, another feature evident from this: because of the tight distribution of error *versus* angle, the controlling inhomogeneity must be considerable, because if it were small, changes in inhomogeneity would have a large percentage effect, which should not be the case in the presence of great inhomogeneity.

4. Since the error-angle distribution is found to occur, then it is evident that, depending upon the direction of the major axis of the vector loop, certain leads will show *QRS*, *T* waves which are, in fact, erroneous compared with the vector component along that lead. Furthermore, the modification of the vector component, from the corresponding component in the presence of a uniform spherical conducting medium, is the result of the inhomogeneity and not related to the cardiac activity. Hence, certain leads must be modified according to the inhomogeneity and should never be used for diagnostic purposes. Furthermore, since it can never be known which are the correct leads without the vector loop, it is evident that the vector loop must be known.

5. In view of the above demonstration of errors in linear electrocardiograms, the problem of the validity of the vector representation also arises.

It should be evident that the ratios of the two branches of the error curve will both continue on a sloping curve of decreasing rate of change below 45°, but in this case the separation of the two increasing and decreasing ratio-angle curves becomes less and less as zero angle is approached and the mean values are indistinguishable from the chance fluctuations about the unity ordinate.

If the vector loop is bound by the same error laws as the linear leads, the remarkably tight distribution actually found in practice should not exist. Furthermore, wide loops, or narrow loops at large angles to one of the vector leads, should not provide correlation with narrow angle linear leads. In all the cases seen, and in comparison with reported cases, not one example of poor correlation with low angle linear leads has been found over all the directions and shapes of planar vector loops, provided that the system of Duchosal and Sulzer has been employed.

It has been found that when the two triangle system was used, poor agreement invariably appeared in sagittal and horizontal planes (Grishman *et alii*, 1951).

The conclusion is evident that the vector loop must be of constant small error over all directions no matter where it is taken, provided the correct plane is used.

It may be shown that the rational system of Duchosal and Sulzer, which is employed in the vectorcardiogram studies reported here, provides two satisfactory conditions: (i) The "cardiac centre" is approximately equidistant from all three lead points on each of the planar vector bipolar leads. (ii) The angles of importance in the vector bipolar leads are (see Figure II) θ_1, θ_2, θ_3. Now θ_3 is common to both vector component leads, and $\theta_1=\theta_2$ by the particular lead structure used. A similar state occurs for the horizontal and sagittal component leads.

Now, whilst it cannot be proved that the theoretical error curve of one lead must follow one branch of the curve of Figure I, if the other lead follows the alternative branch, this has actually been found in practice. If at θ_x, y_1 is the value of one branch and y_2 that of the other, then if the error ratios are computed for two leads at an angle of θ_3, the effective resultant error ratio approximates $(y_1 \times y_2)=$ constant$=1\cdot3$ approximately (see Table I), and hence since $\theta_1=\theta_2$ the other two leads must also follow the same condition.

TABLE I.
(Derived from Figure I.)

θ_x (Degrees)	y_1	y_2	$y_1 \times y_2$
50	2·45	0·49	1·20
55	3·2	0·38	1·22
60	4·4	0·30	1·32
65	5·7	0·23	1·31
70	7·7	0·18	1·40
75	10·0	0·14	1·43
80	15·0	0·11	1·65

Although it is evident that if the lead structure is geometrically correct, then the vector loop can under no conditions show appreciable errors due to inhomogeneity, it is essential to realize that whilst this is the result of the use of two rectangular sets of bipolar leads with one common terminal, the same freedom from error cannot occur in angle bipolar or unipolar leads.

Two other features of importance should be noted.

First, in order to demonstrate the validity of using planar vectors derived from spatial vectors, it should be pointed out that the component parts of a vector give a unique representation of that vector, other components having zero projection on that plane. In view of the demonstrations above of vector accuracy it should be evident that the use of planar vectors for comparative purposes is justified. This is borne out in practice.

Secondly, the question of the comparison between predicted and experimental curves for error-ratio *versus* angle must be considered.

This has been done by calculating the angle relationship for various values of $\delta\theta$. The excellent formal agreement has been shown on the experimental error distribution curve of Figure I. It is evident that the best agreement occurs for relatively large values of $\delta\theta$, and hence considerable measures of inhomogeneity of electrical conductivity. This is as predicted before on theoretical grounds. The best experimental fit to the distribution curve has been found to occur for $\delta\theta = 0 \cdot 15$ radian.

It is therefore concluded that the error angle hypothesis is a correct description of the actual experimental conditions.

A final feature of interest is seemingly of importance. When the ratios of

$$\frac{QRS \text{ obs.}}{QRS \text{ calc.}} \quad \text{and} \quad \frac{T \text{ obs.}}{T \text{ calc.}}$$

were compared, it was found that the T ratio was much larger in all leads than the QRS ratio, even though both show exactly analogous error relationships.

There are two possible explanations which may both play a part in the mechanism. Since the T wave is inscribed at a much slower speed than the QRS wave the Fourier Analysis of the waves shows a major proportion of the T wave to contain low frequency components, whilst the QRS contains much higher frequency components. If the impedance of the body is partly reactive, the impedance will be dependent upon frequency. But if this is the explanation then the ratios of

$$\frac{QRS \text{ obs.}}{QRS \text{ calc.}} \quad \text{and} \quad \frac{T \text{ obs.}}{T \text{ calc.}}$$

should both alter with the period of the waves. This has been found to be not obviously the case. The second possible explanation is that the field conditions, that is either M or r, have been altered, increasing M or decreasing r. It is believed that the latter is the important factor.

Comparison with Reported Cases

Since it has been shown that the rational system of Duchosal and Sulzer provides a correct set of vector loops, the reported cases of these workers have been briefly studied in order to check the occurrence of the above phenomena. In their monograph these workers report 23 cases; in all circumstances these cases have shown the effect, and numerous points from each of the cases have been plotted on the distribution curve (Figure I). A further five cases reported by Duchosal and Grosgurin (1952), including two examples of extrasystoles, have been found to obey the relationship and representative points plotted.

Hence of 68 cases studied, the effect has been found to occur in all, and to be described by the distribution observed in the nine cases studied intensively.

Duchosal and Grosgurin (1952) have plotted modified "cardiac centre" points to correct the calculated electrocardiograms to the observed leads, and in two cases the effective change in direction for best overall correction $\delta\theta$ (for different segments of the loop) has been calculated to be $0 \cdot 148$ (radian), agreeing closely with the value ($\delta\theta = 0 \cdot 15$) estimated experimentally.

Summary and Conclusions

A comparative study of the electrocardiogram and vectorcardiogram in 68 cases (normal and abnormal) has been described.

It has been demonstrated that with certain geometrically defined lead structures, the spatial and planar vectorcardiograms present a good order of accuracy. An explanation of this has been given.

Linear lead electrocardiograms (both unipolar and bipolar) have been shown to obey an error-angle law which is the result of inhomogeneities in the body as an electrically conducting medium. These errors have been shown to depend only upon inhomogeneity and not on specific cardiac abnormalities.

The observed error-angle distribution has been found to agree closely with that predicted in an earlier study on theoretical grounds. The experimental estimate of inhomogeneity based on the present theory has been found to agree closely with that estimated directly from the results of other workers.

The error in any electrocardiogram may occur as a modification of the magnitude of the complexes, or be revealed as a complete change in shape.

It has been shown that correct linear leads may be identified, but only by the use of a correct vectorcardiogram. Hence it is emphasized that a vectorcardiogram obtained by means of the correct lead system gives a superior assessment of the heart's electrical activity, since, depending upon the shape and direction of the locus of the manifest vector, any one or more leads may show the maximum inaccuracy.

It is therefore concluded that:

1. Whenever the axis of the electrical equivalent dipole of the heart approaches 90° to the axis of the lead being used, the error due to inhomogeneity in the electrocardiogram taken from that lead will approach 100% according to a fixed known law.

2. If this angle approaches 90° for any segment of the heart's electrical cycle, then during such interval the error in the electrocardiogram will behave as above; hence such leads will show partly good and partly bad correlation with those estimated from the correct vector loop.

3. It is frequently possible to determine from a given vector loop the error inherent in any lead. This is the case only if the vector loop has been obtained from leads which do not show these errors. If the loop has not been taken from such leads, then the loop itself will be erroneous. A correct loop, however, must obey this law and may be identified by its use.

4. These conclusions indicate that the usual methods of obtaining linear electrocardiograms should not be relied upon. The correct vectorcardiogram method is superior.

5. This law relating error and angle bears no relation to the detail of and assumptions about the nature of the heart's electrical field, except that a cosine term must appear in the numerator of the polar potential-position expression. This is, apparently, always the case.

6. If the correlation between the observed electrocardiogram of any lead and the electrocardiogram calculated from the vector loop is approximately constant and independent of angle, then the vector loop is inaccurate owing to its having been obtained from improperly directed leads. No exceptions to this rule have been found.

7. Depending on the above factors, any lead may show this "error" effect.

8. Hence any lead may be an "optimum" lead. Any true cardiac abnormalities of the electrocardiogram or vectorcardiogram must appear in all leads, weighted by geometrical considerations, and subject to the given error relationship. A correct vectorcardiogram must show, therefore, all significant electrical abnormalities.

ACKNOWLEDGEMENTS

It is a pleasure to record the assistance of the following individuals and departments of the Alfred Hospital: the Electrocardiogram Department and Dr. A. J. Goble and Dr. J. M. Gardiner of the Clinical Research Unit, in compiling the case records for study; Mr. T. O'Connor, in preparing the photographs; Dr. T. E. Lowe, in preparing the manuscript.

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ADDENDUM

In the final paragraph of the "Discussion" mention was made of the possibility that the *T* wave and the *QRS* wave of the electrocardiogram were from different sources, having a similar electrical field distribution but different field conditions. In order to verify this, series of electrocardiograms were obtained

from several patients, and by a procedure of known reactive loading, the internal " source " impedance was calculated for both the *QRS* and *T* waves. From case to case it was found that to account for the different characteristics of the two field conditions (*QRS* and *T*) on the basis of reactive components of source impedance and different frequency alone, it was necessary to assume a body capacitance of value which is much too great to be possible.

It is therefore manifest that since the source impedances are vastly different, the source of the *T* wave is not identical with that of the *QRS* wave. This does not, however, mean that these two components do not share the same source of potential, in part.

ACUTE PORPHYRIA : A STUDY OF SIX CASES[1]

ERIC G. SAINT,[2] ERNEST S. FINCKH[2] AND IAN PARSONS[3]
Melbourne

THE complexities of organic chemistry are bewildering to the clinician, and no field of study has proved more difficult to understand than that of porphyrin metabolism. However, recent work in the laboratories of Lemberg and Legge (1949), Watson (1951) and Rimington (1951) has made it abundantly clear that improved knowledge of porphyrin synthesis and metabolism will offer many vital clues to the complete understanding of many of the problems of hæmatology and chronic liver disease.

The physiological chemistry of the porphyrins has been reviewed by Dobriner and Rhoads (1940) and Welcker (1945). These compounds, first synthesized by Fischer (1937), are comprised of four pyrrol rings united by methene linkages. Their isomeric identity is determined by the type of radical and its position on the pyrrol ring. Of the four theoretical isomers only types I and III occur naturally. The structures of uroporphyrin and coproporphyrins I and III are shown in Figure I. Small quantities of porphyrin are found in the urine and fæces of normal persons. An excess of coproporphyrin I is excreted by patients with obstructive jaundice, infectious hepatitis, post-infective cirrhosis and hæmochromatosis, hæmolytic and pernicious anæmia (Watson and Larson, 1947), and excess of coproporphyrin III in lead poisoning, after the administration of sulphonamides (Rimington and Hemmings, 1939), in aplastic anæmia, alcoholic cirrhosis and pellagra (Beckh, Ellinger and Spies, 1937). In all these conditions porphyrinuria is asymptomatic.

SYMPTOMATIC PORPHYRIA

The symptomatic porphyrias are of intense theoretical interest. Three clinical entities are known :

1. *Congenital (Photosensitive) Porphyria.* This rare inherited disorder was first described by Garrod (Mackey and Garrod, 1921 ; Garrod, 1923, 1936) and has not apparently been reported in Australia. It is characterized by the onset in infancy of bullæ (" *epidermolysis bullosa* ") on the exposed skin, pink staining of the bones, teeth and cartilage, and port-wine coloured urine. It occurs only in males, and

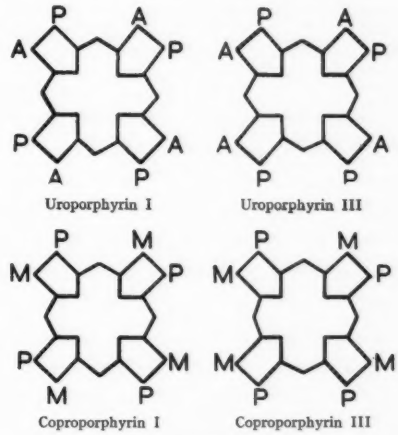

FIGURE I
Diagrammatic representation of structure of uroporphyrin and coproporphyrin I and III. M=methyl ; A=acetic acid ; P=propionic acid

in later life most sufferers develop hæmolytic anæmia. Large quantities of uroporphyrin I and coproporphyrin I are found in the urine. Recent studies with N_{15}-labelled glycine (Gray and Neuberger, 1950 ; London *et alii*, 1950) have shown that the excessive uroporphyrin excretion is due to an anomaly of hæmoglobin synthesis.

2. *Acute Intermittent Porphyria.* This inherited disorder is not excessively rare ; cases have been reported in this country by Derrick (1946) and Hetzel (1949). The classical features of the disease were first described by Günther (1912), and since that date a large literature has grown in Europe and in the United States which has been reviewed by Mason, Courville and Ziskind (1933), Nesbitt

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(1944) and Waldenström (1937). In England there has recently been a spate of case reports: Chandler *et alii* (1939), Discombe and d'Silva (1945), Prunty (1946), Abrahams, Gavey and MacLagan (1947), Petrie (1948), Ashby and Bulmer (1950), Gibson, Harrison and Montgomery (1950), and Grossfield (1951). The outstanding clinical features of acute porphyria are the occurrence of abdominal pain and a variable pattern of psychiatric and neurological manifestations. The urine, which is usually burgundy coloured during the acute episodes, contains an excess of a uro-type porphyrin commonly present in the form of a zinc-complex, and the colourless compound porphobilinogen which is oxidized on exposure to light to form the dark brown pigment porphobilin, and probably uroporphyrin.

3. *Chronic (Mixed) Porphyria.* This disease has many features common to both acute and congenital porphyria. Photosensitive skin lesions develop in adolescence, or even later ("*porphyria cutanea tarda*"), in association with abdominal colic and jaundice due to hepato-cellular necrosis. Neurological symptoms do not occur. Turner and Obermeyer reviewed 14 cases in 1938, and further reports by Taylor *et alii* (1946), Merkelbach (1943), Brunsting and Mason (1946) and Gray *et alii* (1948) have recently appeared. The urinary porphyrin pattern is variable; Waldenström's uro-type porphyrin, uroporphyrin I, and a mixture of coproporphyrin I and III have all been found.

The purpose of this communication is to present the clinical, pathological and biochemical findings in six patients with acute intermittent porphyria, all of whom were seen in Melbourne between January 1950 and June 1952. In two cases the illness proved to be fatal.

METHOD AND MATERIALS

In addition to the usual clinical examination and X-ray and laboratory investigations, a full range of liver function tests—cephalin flocculation test, estimation of serum bilirubin, proteins and alkaline phosphatase content—was performed in three cases. Urea concentration tests were done in three cases. Electro-encephalographic tracings were taken at the height of the attack in two cases.

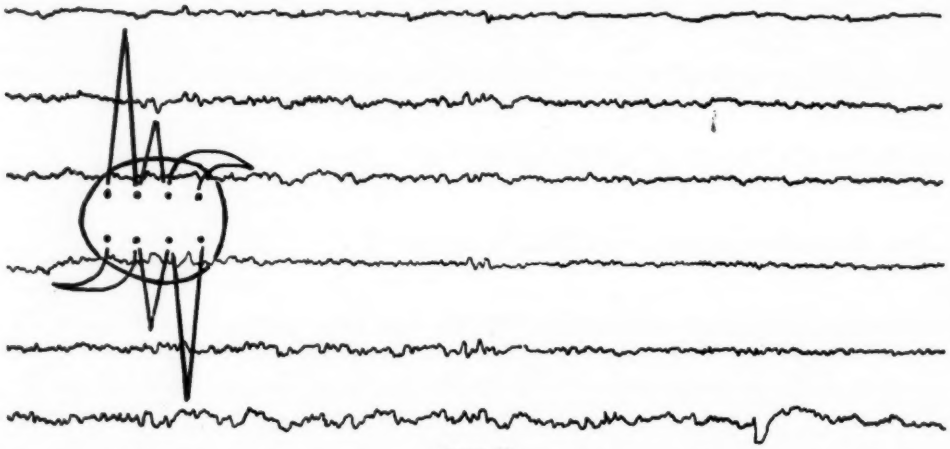

FIGURE II

Electro-encephalogram of a patient with acute porphyria (Case I) taken at the height of the attack. The record shows much muscular artefact. Occipital tracings show mixed α and β rhythms with many slower fluctuations of low voltage (some two per second). Some runs of more irregular activity occur from time to time in the occipital and parietal areas. The frontal records are composed chiefly of irregular β rhythm with some slower fluctuations (around five per second) which are more marked on the left side

The following techniques were used in the examination of the urine of each patient for abnormal constituents.

(i) Spectroscopic examination of the urine by a Hartridge reversion spectroscope was carried out.

(ii) The qualitative test for porphobilinogen with Ehrlich's reagent, described by Watson and Schwarz (1941) was applied.

(iii) The daily excretion of coproporphyrin, obtained by ether extraction of the urine, was studied quantitatively.

(iv) In some cases comprehensive studies of porphyrin excretion by means of spectrophotometric techniques described by Sveinsson, Rimington and Barnes (1949), were performed both at room temperature and after heating. These will be published elsewhere by one of us (I.P.).

CASE RECORDS

CASE I.—A married woman, aged thirty-one years, was operated on at another hospital in November 1951 for recurrent abdominal pain. A congested right ovary was removed. Two days after operation she developed severe abdominal pain and vomited persistently. She became mentally confused and had several epileptic seizures. The urine was burgundy coloured. She was transferred to the Royal Melbourne Hospital twelve days after laparotomy.

On examination she was mentally disorientated. The pulse rate was 110 per minute and the blood pressure was 170 millimetres of mercury systolic and 110 millimetres diastolic. The abdomen was relaxed. There was no muscular paralysis and the reflexes were normal.

After two days she became rational and the blood pressure became normal. She had no further pain or vomiting. She was discharged from hospital three weeks after admission. Since then she has become pregnant but has had no further symptoms.

Investigations.—The hæmoglobin content of the blood was 13·3 grammes *per centum*. The serum bilirubin content was five units *per centum*. Alkaline phosphatase content was 16 King-Armstrong units *per centum*. Serum proteins were normal in amount. The blood urea content was 63 milligrammes *per centum*. The electro-encephalogram (Figure II) was abnormal.

Urine.—Absorption bands were present in the spectrum at 615, 575, 539 and 490 micromillimetres. The Watson and Schwarz test for porphobilinogen gave a strongly positive result. In a specimen of urine obtained at the height of the attack the concentration of Waldenström uro-type porphyrin present was 33 milligrammes per litre, rising to 103 milligrammes after heating. The coproporphyrin concentration was two milligrammes per litre (normal, 120 micrograms per litre). Vivid pink fluorescence of the urine was seen in ultra-violet light.

The urine of the mother and a sister of this patient was examined and was found to contain excessive quantities of coproporphyrin and uroporphyrin. They both enjoyed good health.

Summary.—The patient had acute porphyria with pain, discoloured urine, hypertension, confusion and convulsions; recovery occurred.

CASE II.—A single woman, aged twenty-five years, was admitted to hospital in June 1951. Four weeks previously she complained of severe abdominal pain and was treated with sulphonamides for pyelitis. Pain persisted and spread to the limbs. Diplopia and severe generalized muscular weakness developed and she became mentally disorientated.

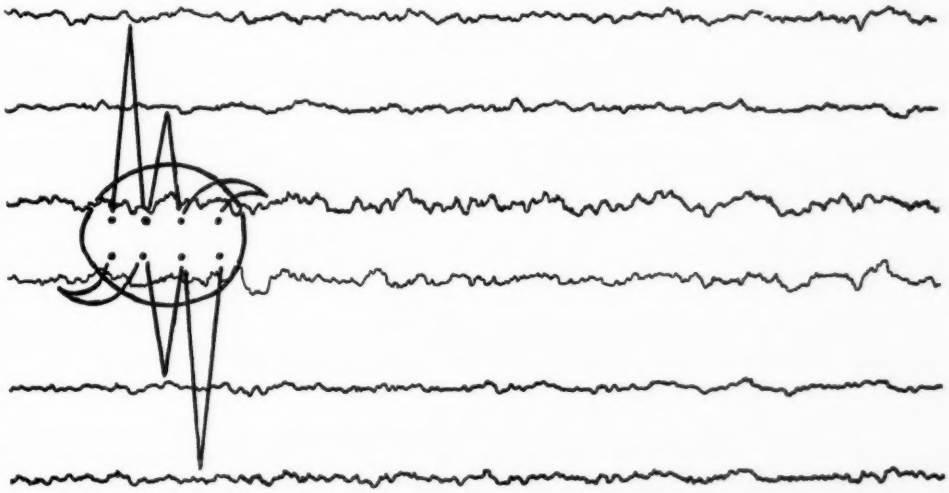

FIGURE IIIA

Electro-encephalogram of a patient with acute porphyria, with confusion and convulsions (Case III), taken at the height of the attack. The record is characterized by much irregular slow activity, of highest voltage in the left anterior frontal region; the low frequencies varied between five and one per second with superimposed β activity. The amplitude varied from time to time and later in the recording of the right-sided occipital record showed most abnormality. Many fluctuations in the interoccipital record were out of phase with the occipital record of one or other side

Her father had died of "senile dementia" and a sister of "transverse myelitis".

On examination total flaccid quadriplegia, facial weakness and bulbar paralysis were present. Respiration was shallow and laboured. She was deeply cyanosed. Signs of collapse were present at the base of the right lung. The patient's temperature was 37·7° C. Her pulse rate was 140 per minute. The blood pressure was 170 millimetres of mercury, systolic, and 110 millimetres, diastolic.

She was transferred to a Drinker respirator and given large doses of penicillin and intravenous injections of aureomycin. She became more deeply cyanosed and died forty-eight hours after admission.

Investigations.—X-ray examination of the chest revealed collapse of the lower lobes of the right and left lungs. The hæmoglobin content was 15·5 grammes *per centum*. The blood urea concentration was 78 milligrammes *per centum*. The serum sodium concentration was 141 milliequivalents per litre. The serum chloride concentration was 92 milliequivalents per litre.

Urine.—Vivid fluorescence occurred with ultra-violet light. Absorption bands were visible in the spectrum at 618, 565 and 543 micromillimetres. The Watson and Schwarz test for porphobilinogen gave a weakly positive result. The concentration of the Waldenström uro-type porphyrin was 19 milligrammes per litre. This was present almost entirely as the free form.

Autopsy Findings.—The lower lobes of both lungs were completely collapsed. The kidneys and spleen were congested, and in the liver lobular markings were more conspicuous than usual. Macroscopically the brain and spinal cord appeared normal. Microscopically the liver showed centrilobular polygonal cell degeneration with dilatation and congestion of the sinusoids in these areas. Chromatolysis, swelling and fragmentation of nerve cells of both the anterior and posterior horns were noted in the dorso-lumbar regions of the spinal cord. The most severe changes were noted in the posterior root ganglia (see Figure IV), where vacuolation and fragmentation with loss of staining properties of nerve cells were extreme. Many of the less affected nerve cells contained masses of fine golden-brown pigment granules.

Summary.—This was a case of acute porphyria with pain, port-wine urine, hypertension, flaccid quadriplegia and bulbar paresis with fatal pulmonary complications.

CASE III.—A married woman, aged forty-one years, was admitted to hospital in October 1950. For five months she had complained of intermittent abdominal pain and vomiting, and on one occasion had been given sulphonamide compounds for a supposed urinary infection. X-ray examination failed to reveal any abnormality in the alimentary tract. She began to have visual hallucinations and became severely depressed. For several weeks prior to her admission to hospital she was under psychiatric observation.

She was comatose on examination. The urine was burgundy coloured. Muscle tone and deep reflexes were normal. She became lucid after four days, but had two major epileptic convulsions. Signs of bronchopneumonia developed which cleared on penicillin treatment. She had no further abdominal pain and was discharged from hospital four weeks after admission.

Investigations.—The hæmoglobin content of the blood was 14·8 grammes *per centum*. The blood urea content was 65 milligrammes *per centum*. The cerebro-spinal fluid was normal. The serum chloride content was 90 milliequivalents per litre. An electro-encephalographic tracing taken shortly after her admission to hospital showed an abnormal pattern (See Figures IIIA and IIIB). Ten days later, when she was recovering, this had reverted to a more normal tracing.

Urine.—The urine fluoresced vividly in ultra-violet light. Only one absorption band was visible in the spectrum at 618 micromillimetres; the remainder of the spectrum was blocked by porphobilin absorption. The Watson and Schwarz test gave a strongly positive result. Serial quantitative studies are discussed below.

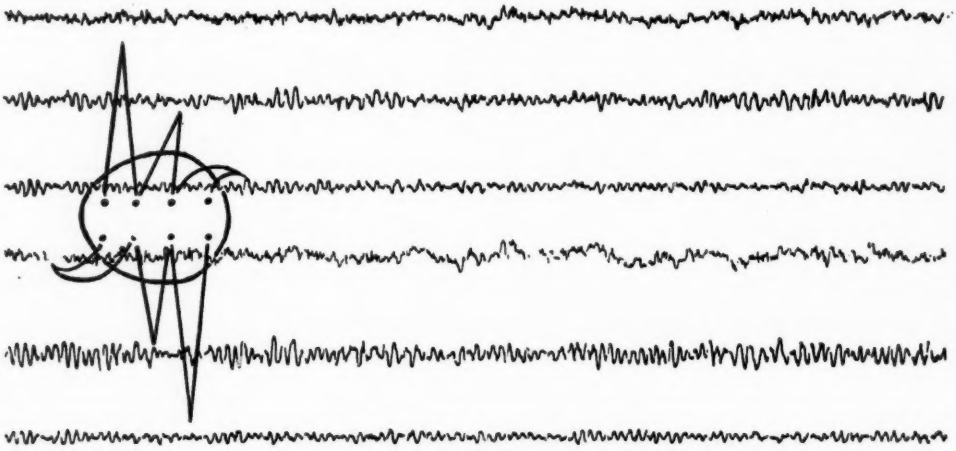

FIGURE IIIB
Electro-encephalogram of same patient ten days later when symptoms had subsided. The record had changed completely, having reverted almost to normal. Some slow compound low voltage fluctuations were seen, in the frontal regions. The α rhythm was of higher voltage in the parietal regions than elsewhere

Summary.—This was a case of acute porphyria, the patient presenting with acute psychosis, abdominal pain, port-wine urine, coma and convulsions.

CASE IV.—A twenty-seven years old Russian migrant was admitted to hospital in June 1952. For almost a year she had complained of intermittent abdominal pain. For five weeks central abdominal pain had been severe and accompanied by intractable vomiting.

On examination she was mentally confused. Her pulse rate was 98 per minute. Her blood pressure was 180 millimetres of mercury, systolic, and 120 millimetres, diastolic. The abdomen was lax. There was no muscular weakness or sensory loss. Both ankle jerks were absent, but the remaining reflexes were normal.

She became irrational and maniacal, requiring heavy sedation with paraldehyde. She had several epileptic seizures. In view of the vomiting several litres of normal saline were given intravenously and she was fed by a slow intragastric milk drip. Signs of collapse and infection of the left lung developed and she died two weeks after admission.

Investigations.—The hæmoglobin content of the blood was 16·2 grammes *per centum*. The cerebrospinal fluid was normal. The blood urea concentration was 78 milligrammes *per centum*. The serum sodium concentration was 135 milliequivalents per litre, serum potassium 4·9 milliequivalents, and serum chloride 73 milliequivalents. The electrocardiogram showed a prominent *Q* wave in leads I, V4 and V6 and abnormalities of *ST*1, *ST*v4 and *ST*v6.

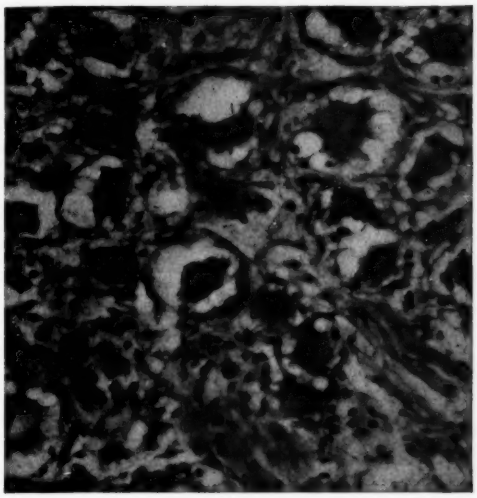

FIGURE IV
Section of a thoracic posterior root ganglia from a fatal case of acute porphyria (Case II, female aged twenty-five years). There is some pigmentation with advanced vacuolation, chromatolysis and nuclear degeneration of the nerve cells. Haematoxylin and eosin, × 265

Urine.—The urine fluoresced vividly with ultraviolet light. The Watson and Schwarz test gave a strongly positive result. The total urinary porphyrin excretion was 7·8 milligrammes per litre (coproporphyrin 2·0 milligrammes per litre). The fact that absorption bands in the spectrum were present at only 575 and 540 micromillimetres indicated that porphyrin was present almost entirely as the metal complex.

Autopsy Findings.—The whole of the left lung and a portion of the right lower lobe were collapsed. The kidneys were congested. The liver was normal in size, but dark reddish brown in colour and showed many lighter coloured circumscribed areas measuring one to three millimetres in diameter on the outer and cut surfaces (see Figure V). The brain and spinal cord were macroscopically normal.

Microscopically it was noted that the bulk of the liver cells were pale and eosinophilic, and had rather small dark nuclei; the sinusoids were dilated with blood. By contrast the macroscopically pale areas were composed of larger more basophilic cells with vesicular and sometimes multiple nuclei. This pallor was in part accounted for by the relative bloodlessness of the sinusoids. The appearances suggested widespread degenerative changes with distinct islands of regenerating parenchymal cells.

In the brain patches of nerve cells containing free golden-brown pigment alternated with unaffected areas (see Figure VI). Similar but less marked changes were noted in the anterior and posterior horn cells of the spinal cord. Many of these cells stained poorly and were swollen or fragmented.

Summary.—This was a case of acute porphyria characterized by recurrent abdominal pain, port-wine urine, confusion and convulsions, and fatal pulmonary complications.

CASE V.—A married woman, aged thirty-one years, was admitted to hospital in August 1951. Apart from occasional attacks of asthma and biliousness she had been in good health until June, when she complained of severe pain in the abdomen, back and limbs. She was treated with sulphonamides for pyelitis, but intractable vomiting necessitated intravenous fluid replacement. She became mentally confused, incontinent of urine, and developed weakness of the arms, trunk and legs. For a few days she was slightly jaundiced. The urine was burgundy coloured.

On examination she was disorientated, and her breathing was laboured. Her temperature was 37·6° C., and her pulse rate was 160 per minute. Her blood pressure was 160 millimetres of mercury, systolic, and 110 millimetres, diastolic. The abdomen was lax.

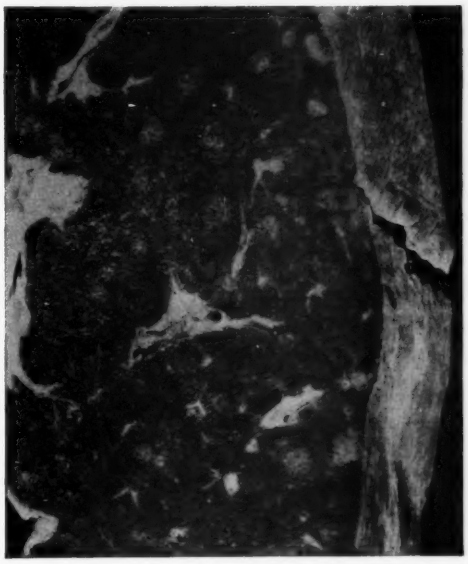

FIGURE V
A close-up view of the macroscopic appearance of the cut surface of the liver from Case IV. The pale circumscribed areas were less vascular than the remainder and comprised larger, often multinucleated regenerating cells

Speech had a nasal quality and was slurred. She had a complete flaccid quadriplegia and the reflexes were absent. Analgesia to pain was noted in the proximal portion of the upper limbs.

Diaphragmatic paralysis developed shortly after her admission and she was placed in a respirator and fed by intragastric drip. Penicillin, 2,000,000 units daily,

was administered. Pethidine was given as an analgesic. Folic acid, 10 milligrammes, vitamin B_{12}, 50 microgrammes, and vitamin B_1, 100 milligrammes, were given each day.

The bulbar weakness became less after two days and she soon became mentally lucid. After four days her respiration had improved to such an extent that she was allowed out of the respirator for a short period every four hours. After two weeks she was transferred

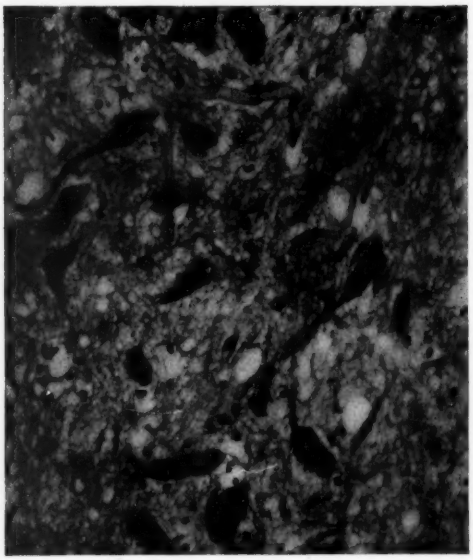

FIGURE VI
Section of cerebral cortex from a fatal case of acute porphyria (Case IV, female aged twenty-seven years). Many nerve cells contain masses of yellow-brown granules. These can be seen extending along the axon of the cell in the upper left-hand corner of the figure. Haematoxylin and eosin, × 265

back to the general ward. Paresis was then restricted to the rhomboids and extensors and flexors of the upper limbs. After a course of graded exercises supervised by the physiotherapists she could eventually walk unassisted, and was discharged from hospital in November with only some residual weakness of the intrinsic muscles of the hands. [1]

Of relevant interest was the information that her mother and a sister of her mother's had suffered similar but less severe symptoms.

Investigations.—X-ray screening of the chest confirmed the total paralysis of the diaphragm. The hæmoglobin content was 13·8 grammes *per centum*. Reticulocytes numbered less than 1% of the red cells. The cerebro-spinal fluid was normal. Tests of liver function gave normal results. The blood urea content was 53 milligrammes *per centum*. Nerve biopsy (see Figure VII) showed extensive and patchy demyelination.

Urine.—The urine fluoresced vividly in ultra-violet light. The Watson and Schwarz test gave a strongly positive result. Absorption bands were seen in the spectrum at 579 and 546 micromillimetres, indicating that porphyrin was present entirely as a metal complex. Quantitative studies showed a porphyrin concentration of five milligrammes per litre, increasing to 35 milligrammes after heating. Daily urinary porphyrin excretion was studied in this patient over a period of three months (see below).

A number of the patient's relatives were examined. Her mother's sister, who had no symptoms of porphyria, produced a dark brown specimen of urine with absorption bands at 595 and 553 micromillimetres (acid porphyrin); the Watson and Schwarz test gave a positive result and she excreted 3·7 milligrammes total porphyrin per litre.

Summary.—This was a severe case of acute porphyria characterized by abdominal pain, port-wine urine, hypertension and severe bulbar and peripheral muscular paresis. Recovery occurred after two weeks in a respirator.

CASE VI.—A woman, aged fifty-six years, had a "nervous breakdown" in 1941 when she temporarily lost the use of her right arm. In January 1950 she complained of a pain in her left leg and became irritable and slightly eccentric in her behaviour. She complained of vague abdominal pain and was admitted to hospital in June 1950.

FIGURE VII
Section of a nerve biopsy taken from a female, aged thirty-one-years, at the height of an attack of acute porphyria. Subsequent recovery was complete. Demyelination is advanced. Osmic acid, × 430

In hospital she became unrestrainedly violent and had several convulsions. The blood pressure was 210 millimetres of mercury, systolic, and 130 millimetres, diastolic. The urine was port-wine coloured.

Investigations.—The hæmoglobin content was 14·3 grammes *per centum*. Blood urea concentration was 89 milligrammes *per centum*. During the acute phase the serum sodium concentration was 128 milli-

[1] This patient was seen again in August 1952, when she was in excellent health without any residual motor weakness or sensory change.

equivalents per litre and serum potassium 7·4 milliequivalents. At this period the patient had obvious oliguria (daily volume of urine approximately 250 millilitres). Ten days later a diuresis occurred (3,000 millilitres of urine daily); the serum sodium concentration rose to 140 milliequivalents and the serum potassium fell to 3·3 milliequivalents per litre.

Urine.—The urine fluoresced with ultra-violet light. Absorption bands were seen in the spectrum at 616, 577, 541 and 516 micromillimetres, indicating the presence of both free and combined uroporphyrin. The Watson and Schwarz test gave a strongly positive reaction.

Summary.—This was a case of acute porphyria in an elderly patient with presenting symptoms suggesting hysteria; recovery occurred.

DISCUSSION

That six cases of acute porphyria were encountered in eighteen months indicates that the disease in Australia is more than a rare clinical curiosity. It is possible that local genetic patterns are responsible for the curious geographical distribution of cases in the world, for the paucity of case reports in the British Isles, for example, has always been in striking contrast to the prevalence of acute porphyria in Scandinavian countries. Five of our own patients were of British stock and one was a central European.

Clinical Features

Two characteristic features of acute porphyria are that it is predominantly a disease which affects females, and that symptoms usually commence in the third or fourth decade of life. It is also an inherited error of metabolism—a Mendelian dominant according to Waldenström and Vahlquist (1944). The maternal relatives of two of our patients were found to be excreting abnormal quantities of porphyrin and porphobilinogen, and relatives of two other patients died of maladies which may well have been porphyria.

Although the symptomatic manifestations of acute porphyria are protean, a definite pattern is discernible in most cases. Recurrent abdominal pain and discoloration of the urine are almost invariable events; but mental aberration and muscular paresis may later dominate the picture to the exclusion of all else. In consequence it is not unusual for patients with porphyria to appear first before the surgeon as an abdominal emergency, or before the neurologist as a problem of peripheral neuropathy, or before the psychiatrist for the treatment of an obscure psychosis.

Abdominal pain and vomiting may be a patient's sole complaint for several months. A patient of Nesbitt and Watkins (1942) had no less than eight attacks in twelve months. The pain has a wide area of radiation in the abdomen and back, and is commonly experienced also in the limbs. A point of great practical importance in differentiating pain of this cause from that due to pyelitis, biliary disease, pancreatitis, duodenal ulcer or ruptured ectopic pregnancy is the complete absence of abdominal tenderness or rigidity. In this regard the pain of porphyria has affinities with the colic of lead poisoning. The cause of the pain is quite obscure, although it is possibly of some significance that the stomach of the patient of Chandler and his colleagues (1939) at laparotomy was seen to be in a state of intense spasm. Obstinate constipation frequently accompanies the abdominal pain and radiological investigations have shown dilatation and ileus of portions of the alimentary tract (Nesbitt, 1944).

With few exceptions (Backer-Gröndahl, 1935) the urine shows a burgundy or port-wine discoloration at the height of the attack of abdominal pain. This discoloration is due to the presence of large quantities of porphobilin and porphyrins. A normal coloured urine, however, in no way vitiates a clinical diagnosis of porphyria. The fresh specimen may darken on standing for twenty-four hours or more, due to the conversion of porphobilinogen to the coloured porphobilin. Three simple tests are of value in establishing a diagnosis: fluorescence with ultra-violet light, the Watson and Schwarz test and spectroscopic examination.

Transient jaundice was observed in three patients at the peak of the attack. Since anæmia and reticulocytosis were conspicuously absent, this excess of bile pigment did not appear to be the result of hæmolysis. Nor did it seem likely that bilirubin was one of the incidental products of abnormal hæmoglobin metabolism, as is the case in chronic porphyria. It seems most likely that the jaundice was due to ischæmic focal necrosis of the liver.

Vascular phenomena were indeed an integral part of the clinical picture. Significant arterial hypertension (in one case 130 millimetres of mercury diastolic) subsiding with remission of visceral and neurological symptoms, was present in five patients. Associated with this elevated blood pressure was a moderate degree of nitrogen retention (blood urea 53 to 89 milligrammes *per centum*). Tachycardia was invariably present, quite out of proportion to the mild pyrexia that was usually found. The commonest electrocardiographic finding was a sinus tachycardia. One patient showed a $Q1$ wave with elevation of the $ST1$ segment.

Eliaser and Kondo (1942) have described similar changes which they attributed to coronary artery spasm.

Since abdominal pain may be the only manifestation of porphyria for many months and since the abnormal colour of the urine may be missed, it is not surprising that the disease may escape detection for long periods. It was not until the supervention of psychotic or neurological symptoms that a diagnosis was made in many of these cases. So protean are these neuro-psychiatric manifestations that porphyria has been described by Waldenström as "*la petite simulatrice*".

Confusional states and convulsions occurred in four of these patients, two of whom had highly abnormal electro-encephalographic tracings. The frequency of these toxic cerebral symptoms has been recorded by others (Harbitz, 1924; Turner, 1938; Golden, 1943; Nesbitt, 1944). Frank psychosis such as depression with suicidal tendencies (Eichler, 1932) or schizophrenic symptoms (Freeman, 1951) has also been described.

Neurological manifestations range from a limited mononeuritis to a fatal ascending paralysis of the Landry type (Palmer, 1940). Physical signs may be limited to asymmetric loss of a few deep reflexes; or the patient may have a total flaccid quadriplegia. Evidence of involvement of the cranial nerves and bulbar centres—diplopia, nystagmus, ptosis, palatal weakness and dysarthria—is common (Cases II and V). Sensory loss does not appear to be a very prominent feature of the neurological syndrome, and when present is of patchy asymmetrical distribution (Case V). Clearly, then, this "*petite simulatrice*" is a trap for the unwary, for superficially at least porphyria may be difficult to differentiate from the organic psychoses, anxiety-hysteria, poliomyelitis, the peripheral neuropathies, the Guillain-Barré syndrome (Saint, 1951), and familial periodic paralysis. However, the onset with symptoms of abdominal pain and discoloration of the urine should be a "divining rod" in clinical diagnosis.

Investigations

Elevation of the serum bilirubin level occurred in three patients and in one the serum alkaline phosphatase was raised, indicating impaired liver function. The elevation of the blood urea level in the acute stages has already been noted. In the three patients on whom serum electrolyte studies were made, low concentrations of serum sodium and chloride were noted. In part this hypochloræmia and hyponatræmia may have been due to continued vomiting, but the evidence in Case VI, in which this electrolyte pattern occurred in association with oliguria, suggests that a renal vascular mechanism is operating during the acute attacks of porphyria. Grossfield (1951) found that the results of Power-Kepler tests were normal in his patient, indicating that acute adrenal insufficiency is an unlikely cause of serum electrolytic anomalies.

The findings in the urine of these patients were similar to those recorded by other workers. Vivid fluorescence with ultra-violet light was invariably observed, and the Watson and Schwarz test, which depends on the insolubility of the pigment produced with Ehrlich's reagent in the chloroform phase, always gave a positive result. The position of the absorption bands seen spectroscopically varied according to whether or not the Waldenström uroporphyrin was present predominantly as the free substance or as the zinc complex. Free porphyrin gives spectrum bands at approximately 615, 565, 539 and 504 micromillimetres. Bands are seen only at 575 and 541 micromillimetres in the case of the metalloporphyrin; these could be misconstrued as being due to oxyhæmoglobin, but the absence of collateral evidence of hæmaturia, and the fact that after acidification of porphyrin-containing urine a striking change of position and intensity of bands occurs, should clarify the issue.

Quantitative studies have shown that very variable amounts of porphobilinogen, the Waldenström uro-type porphyrin, and coproporphyrin (both I and III) were excreted. It is the opinion of most workers that excretion of coproporphyrin is of no significance in the production of symptoms. Our findings would also indicate that there is no correlation between the amount of porphobilinogen or uroporphyrin excreted and the severity of symptoms. In this latter respect Case III is of extreme interest (see Figure VIII); at a time when symptoms were subsiding there was a sudden huge increase in the amount of porphyrin excreted in the urine without any concomitant relapse of symptoms. Quantitative studies were performed on the urine of Case V for a long period, and although diminution of porphyrin excretion paralleled symptomatic improvement (Figure IX), on her discharge from hospital she was still excreting grossly abnormal quantities of porphyrin. Clearly, these urinary findings are but an approximate index of an unknown metabolic anomaly.

Pathology

The pathological findings in acute porphyria have been extensively reviewed by Mason,

Courville and Ziskind (1933). Despite the diffuse clinical manifestations, there is often little to be seen at autopsy. In patients with bulbar symptoms pulmonary complications are the most common cause of death; extensive pulmonary collapse was seen in our own two fatal cases.

Degenerative changes have been described in the liver and kidneys. Our own findings are of interest; in Case II well-marked centrilobular necrosis was seen in the liver, and in Case IV there was evidence of generalized hepatic cell degeneration with localized areas of regeneration visible macroscopically. The liver in both cases fluoresced vividly with ultra-violet light, and in Case IV large quantities of uroporphyrin were extracted.

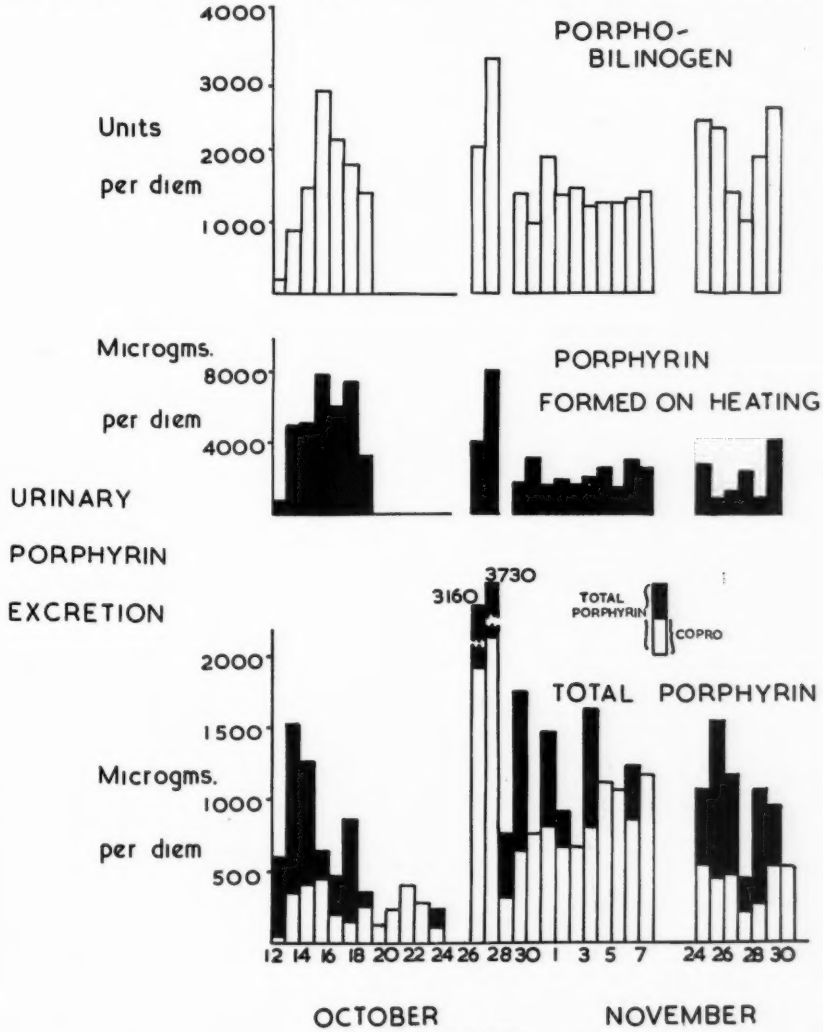

FIGURE VIII

Daily excretion of porphyrin and porphobilinogen in a case of acute porphyria (Case III). The extreme rise in the total porphyrin excretion which occurred on October 26 was unaccompanied by any clinical relapse

The histological changes seen in the central nervous system are non-specific in character (Courcoux *et alii*, 1929; Baker and Watson, 1945; Denny Brown and Sciarra, 1945). In our own material widespread chromatolysis of

nerve cells of both the anterior and posterior horns, and of the posterior root ganglia was seen, as well as diffuse demyelination and the deposition of an unusual golden-brown pigment. These pathological findings do not help us to understand the fundamental nature of the genetically determined biochemical abnormality in acute porphyria, which remains quite obscure. It is conceivable that studies with isotopes may ultimately supply this essential knowledge. Clinically there are striking affinities between acute porphyria and two other conditions—lead poisoning, which is known to be associated with abnormal coproporphyrin excretion, and *periarteritis nodosa*, a disease of small arteries and arterioles. In all three diseases, pain, tachycardia, hypertension, neuropathy and encephalopathy are significant clinical features. Many of the clinical and pathological features of acute porphyria are, we believe, explicable on the basis of vascular involvement, as follows: (i) The transient hypertension and oliguria point to an ischæmic renal vascular mechanism. (ii) The focal necrosis seen in the liver also is most probably of ischæmic origin. (iii) Both Watson and Baker, and Denny Brown and Sciarra noted that demyelination in the central nervous system had a perivascular

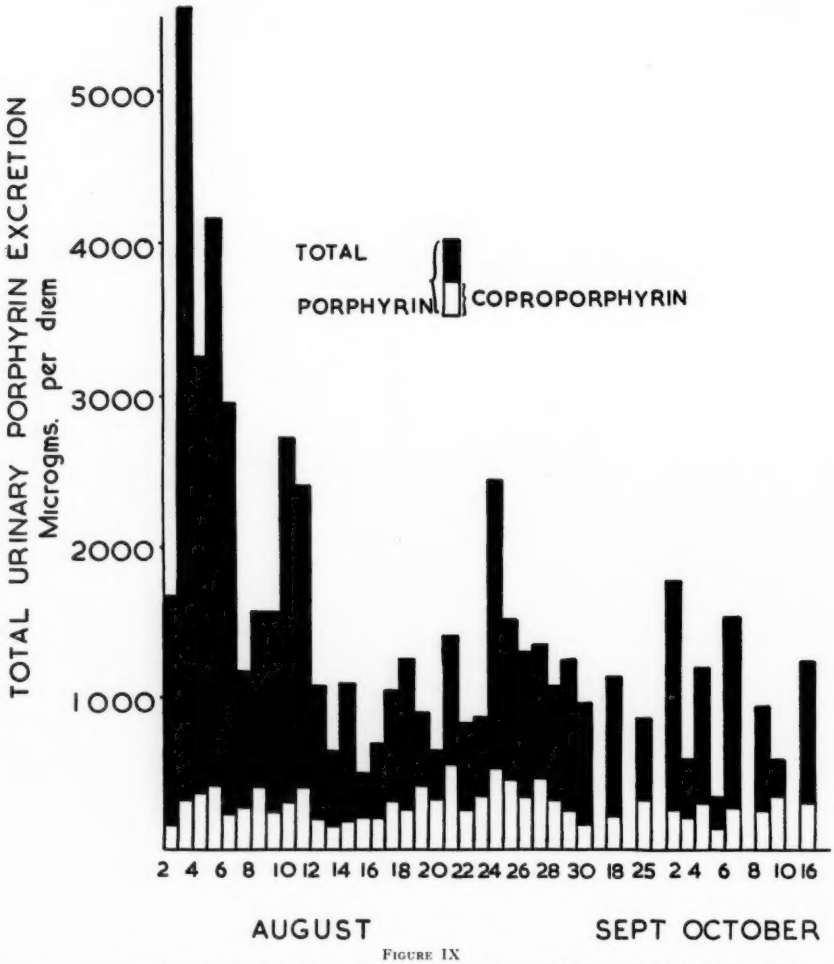

FIGURE IX

Daily porphyrin excretion in a patient with acute porphyria with severe neurological complications (Case V). Although a gradual fall is noted, after two months she was still excreting highly abnormal quantities. This does not include porphyrin formed on heating

distribution. (iv) Waldenström (1937) noted spasm of the retinal arteries in some of his patients.

Prognosis and Treatment

Two of our six patients died as a result of pulmonary collapse and infection. In the literature the overall mortality rate has been of the order of 70%; when symptoms have consisted only of abdominal pain, a fatal issue has been unusual, but when weakness of the respiratory muscles or bulbar symptoms have supervened, death due to pulmonary complications has usually followed.

Our experience with cases of acute porphyria in which severe neurological complications are present leads us to believe that a considerable measure of recovery of neuro-muscular function is possible, provided the patient can be kept alive over the acute phase of the illness. The therapeutic problem is strictly comparable to that encountered in the management of severe tetanus (Saint, Joske and Stubbe, 1952). Weakness of the respiratory muscles must be recognized at an early stage and the patient should be nursed in a mechanical respirator for as long a period as is necessary; all possible measures should be undertaken to prevent pulmonary complications, including the routine administration of both streptomycin (two grammes daily) and penicillin (2,000,000 units daily), and frequent aspiration of the accumulated infected secretions of the nasopharynx. If these secretions are at all dangerously abundant, tracheotomy should be resorted to as an immediate emergency. Our success with the patient in Case V who recovered eventually from a severe ascending paralysis and who remained free from pulmonary infection after two weeks in a respirator, encourages us to believe that the immediate prognosis of acute porphyria may not of necessity be so grave as has hitherto been supposed.

At the same time attention must be paid to the maintenance of a good state of nutrition. For this purpose an intragastric drip delivering a reinforced milk mixture has proved of great use.

The variety of vitamins and other therapeutic agents that have been used in the treatment of porphyria reflects our ignorance of the ultimate nature of the disease. Methionine (Prunty, 1946), pantothenic acid (Davies, 1949), and riboflavine (Stich, 1950) have all been used without demonstrable value. In Case V the patient was given folic acid and vitamin B_{12} when reports of Pimento de Mello's work (1950) on the relationship of these substances to coproporphyrin appeared; they were without effect.

It is well known that barbiturates (Waldenström, 1937) and sulphonamides (Rimington and Hemmings, 1939) increase porphyrin excretion, but whether acute "toxic" porphyria caused by these drugs is a clinical entity is a matter for debate. Although sulphonamides had been given to some of our patients prior to their admission to hospital, in retrospect it was apparent that in all instances pain and discoloration of the urine had preceded the exhibition of the drugs. One patient (Case I) was given provocative doses of barbiturates during her recovery, without recurrence of symptoms and without significant elevation of porphyrin or porphobilinogen excretion. Nevertheless, in view of our uncertain knowledge, it would be foolhardy to do other than avoid the use of either sulphonamides or barbiturates in these cases. For severe pain, therefore, morphine or pethidine was invariably prescribed; for restlessness paraldehyde was always given, and for mild sedation, chloral was eminently suitable.

In view of the possible vascular basis underlying the symptomatology of acute porphyria it would seem reasonable to give the sympathetic ganglion blocking agents (hexamethonium compounds) a therapeutic trial at a future date.

SUMMARY

1. Acute porphyria appears to be not uncommon in Australia. Six cases occurring in patients seen in Melbourne between 1950 and 1952 are reported. In two the illness was fatal.

2. Although clinical manifestations are protean, a diagnosis can be made on a pattern of abdominal pain, hypertension and port-wine coloured urine. Many patients have symptoms of hysteria or psychosis, and severe ascending paralysis commonly occurs.

3. As simple laboratory aids to diagnosis, fluorescence of the urine with ultra-violet light, and characteristic absorption bands seen spectroscopically are important. The Watson and Schwarz test with Ehrlich's reagent for porphobilinogen is pathognomonic of acute porphyria and can be performed in any clinical side room.

4. Transient elevation of the blood urea and serum bilirubin levels, abnormalities in the serum electrolyte pattern, and abnormal electroencephalographic tracings were seen in patients who were severely ill.

5. Necrotic changes in the liver, chromatolysis and pigmentation of nerve cells, and patchy

demyelination in the brain and peripheral nerves were noted at necropsy. Many of these pathological changes were felt to be explicable on a basis of vascular spasm.

6. Two patients died as a result of severe pulmonary complications.

7. There is no specific therapy for acute porphyria. The most important principles of treatment are fluid replacement and intragastric feeding, the prompt use of the mechanical respirator in severaly paralysed patients, and the use of antibiotics and, where indicated, tracheotomy to prevent or remedy pulmonary infection. The use of barbiturates and sulphonamides should be avoided.

ACKNOWLEDGEMENTS

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RUPTURE OF A CORONARY VESSEL: A REPORT OF TWO CASES[1]

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Hæmorrhage from rupture of the heart or rupture of an aneurysm of the aorta into the pericardium is one of the commonest causes of hæmopericardium and, indeed, if hæmopericardium is suspected or diagnosed, it is usually in this group that the ætiological factor is found. In some cases, however, a hæmopericardium may result from rupture of a coronary artery or, more rarely, a coronary vein (Maclagen, 1845; Pepere, 1906).

Although this condition of rupture of a coronary vessel is distinctly uncommon, there are over thirty references easily available in the literature. These are to be found in some articles specially devoted to the condition, but most of them are found in general reports of groups of cases of cardiac disease. Many of the cases described go back for more than a century; for example, cases were recognized by Morgagni (1761), Feigneux (1740), Fischer (1740) and Kramer (1732) in the eighteenth century. Three cases have been recorded in Australian journals (Youl, 1872; Kesteven and Verco, 1920; Edwards, 1928).

In view of the infrequency of the condition, a report of two further cases is given here.

Case Histories

Case I

A female patient, aged fifty-nine years, was admitted to hospital in a shocked condition. She had been well until five days previously, when suddenly she began to have pain in front of the chest and between the breasts. The pain spread up into the neck and down both arms. This pain began during the night. It persisted until the morning, when it became less severe. During the next four days she was in bed most of the time, but got up to cook meals for the family. On the afternoon of her admission to hospital she got out of bed at 4.30 p.m.; when her husband arrived home at 5.30 p.m. she was lying on the couch complaining of severe pain over the chest and down the arms. The husband said she was very blue.

She had had an operation for removal of the gall-bladder a year before, but apart from this had had no significant illness.

On examination the skin was cold and the lips were cyanosed. The capillary return was poor. The pulse rate was 120 beats per minute; the sounds were very faint and no murmur was audible. Respirations were shallow but regular. No crepitation was audible at the lung bases. The liver was tender on palpation and there were three fingers' breadth of liver dulness below the costal margin. There was some pitting

Figure I
The outer surface of the heart in Case I, showing subpericardial bruising surrounding the ruptured vessel

œdema of the legs, but no œdema over the sacrum. The veins in the neck were not distended.

A provisional diagnosis of cardiac infarction was made. Appropriate treatment was given, but death occurred six hours after admission.

Post-mortem examination was performed twelve hours after death. Post-mortem staining was present.

The pericardial sac was thin and distended by blood-clot, which appeared as a blue translucency. About

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140 millilitres of clot were present. The heart was normal in size. The muscle showed no scarring and there was no hypertrophy. The cavities and endocardium were normal and the *foramen ovale* was closed. The coronary arteries showed patchy intimal thickening. The source of the hæmopericardium was an area of hæmorrhage on the lateral surface of the left ventricle. Here the epicardium was bulged and the underlying fat was infiltrated with blood (Figure I). Some hæmorrhage was present at one point in the superficial layer of the muscle of the ventricle, but there was no infarction and the ventricle had not ruptured (Figure II). The source of the hæmorrhage was a small coronary vessel arising from the marginal branch of the left coronary artery.

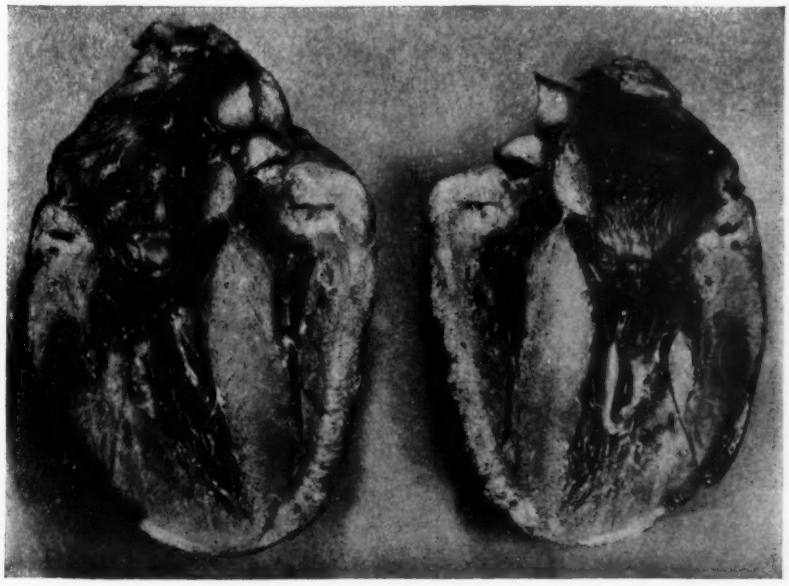

FIGURE II
A section passing through the ventricles of the heart in Figure I showing that the extravasation of blood is not confined to the subpericardial connective tissue, but also involves a superficial layer of cardiac muscle. No infarction is present

Histologically, there was no evidence of infarction of the muscle. There was a well-developed hæmorrhage, localized in the superficial muscle and beneath the epicardium. This communicated with one of the coronary branches. It was not possible to determine with certainty whether there had been an aneurysm of the vessel, however; no evidence of this could be found.

Other vessels throughout the body—renal, splenic and superior mesenteric arteries—showed irregular atheromatous change; the pulmonary arteries were normal. There was some œdema of the lungs; both bases were congested, but otherwise these organs were normal. The liver was enlarged, its weight being 1950 grammes. The spleen was somewhat enlarged (227 grammes) and was congested. No other abnormality was found.

Case II

A male patient, aged seventy-one years, was admitted to hospital and gave the following short history. Eighteen years prior to admission he had had an operation for drainage of an empyema of the right pleural cavity and, recently, he had suffered from some intermittent claudication of the legs. There had been no other previous illnesses. Twelve hours prior to his admission to hospital he had an attack of retrosternal discomfort which lasted for several minutes. Six hours later, while walking along the street, he experienced a severe gripping retrosternal pain which persisted up till the time of examination. After the onset of the pain he was able to walk home, a distance of some 50 metres. The pain did not radiate and he was only slightly short of breath.

On examination he had a pulse rate of 180 beats per minute and the systolic blood pressure reading was 175 millimetres of mercury and diastolic pressure 130 millimetres. The heart appeared slightly enlarged and the sounds were regular. No murmur was heard. There was no jugular venous congestion or peripheral œdema, but fine crepitations were audible at both lung bases. A diagnosis of myocardial infarction was made.

Electrocardiographic examination revealed an auricular flutter with a 1 : 2 ventricular response. This examination was repeated on the following day, when the cardiac rhythm had returned to normal, and there was evidence of a recent anterolateral cardiac infarction.

Appropriate therapy was instituted and the patient's condition appeared to be improving slowly. However, on the evening of the fourth day the patient suddenly sat up in bed, vomited and complained of agonizing abdominal pain. Morphine and oxygen were administered, but he died in a matter of minutes.

Post-mortem examination was performed twelve hours after death. Post-mortem staining and *rigor mortis* were present.

The pericardium was distended with recently clotted blood (Figure III). The heart was slightly enlarged and showed bruising under the epicardium along the course of the anterior descending branch of the left coronary artery. Further examination showed that a branch of this vessel had ruptured, giving rise to the hæmopericardium. The coronary arteries showed a patchy atheroma. At the apex of the left ventricle there was evidence of a recent cardiac infarction; there was no rupture of the myocardium. The cavities of the heart appeared normal.

The aorta showed widespread atherosclerotic changes with ulceration in its lower half. Renal, splenic and superior mesenteric vessels showed patchy atheroma; the femoral veins and pulmonary arteries were normal.

There were extensive adhesions in the right pleural cavity and some pulmonary œdema, but otherwise the lungs were normal.

The only other abnormality discovered was a large vesical calculus.

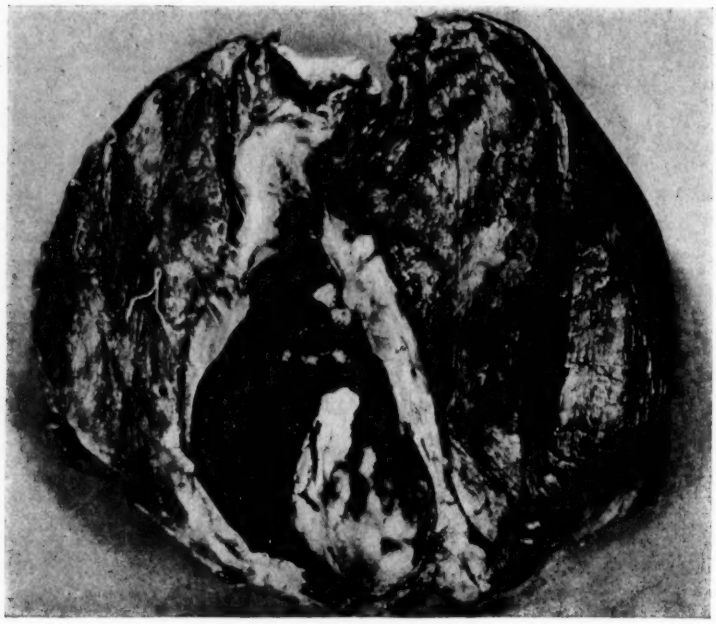

FIGURE III
The thoracic viscera of Case II viewed from the anterior aspect. Some of the parietal pericardium has been cut away and the pericardial cavity is seen to be distended with blood clot

COMMENTARY

Rupture of a coronary artery may occur in cases of aneurysm of the vessel. It may, however, occur in the absence of aneurysmal dilatation and in these cases well-developed arterial disease is usually present. A third group comprises those in which there is an embolism of the coronary artery. Rupture of a coronary artery in a myocardial abscess has been reported (McLagan, 1928). Syphilis does not appear to be an ætiological factor and traumatic rupture of the vessel does not fall within the scope of the present discussion. In some cases no definite ætiological factor has been found.

Most patients are above the age of fifty and males appear to be affected more frequently than females. Rupture of an aneurysm occurs in a younger age group and has been observed in children.

The left coronary artery and its branches are usually involved; it is well known that atheromatous change occurs more frequently in the left than in the right vessel. The vessel may rupture in any part of its extent.

Since the vessels lie for the most part on the superficial aspect of the heart, the thickness of the heart wall is not necessarily involved; often only a small lesion in and around the vessel is apparent. There is usually hæmorrhage into the epicardial tissues and the subjacent layers of the myocardium may be involved. There may be a myocardial infarction in association with, but distal to, the vascular lesion. Case II is a further example of this.

It is noteworthy that both these patients complained of symptoms suggesting ischæmia of the myocardium for several days prior to the terminal episode. This suggests that possibly the vascular lesion, leading ultimately to rupture, was causing some occlusion of the artery and consequent myocardial ischæmia producing, in one case, a frank myocardial infarction.

Both patients exhibited a sudden collapse prior to death. One succumbed almost immediately; the other, some ten hours later. Clearly, in the former case there was a sudden outpouring of blood into the pericardium. In the latter case, however, it is more difficult to correlate the clinical with the pathological features. It is extremely unlikely that the hæmopericardium had existed for more than a few hours. Possibly, some of the terminal symptoms may have been related to the small degree of hæmorrhage into the subjacent myocardium. This case emphasizes the difficulty in clearly associating any particular pathological lesion with precordial pain.

SUMMARY

1. Two cases of rupture of the coronary artery are described. In one of these cases there was an associated myocardial infarct.

2. The ætiology of the condition is discussed and a correlation between the clinical and autopsy findings is attempted.

3. Reference is made to the fact that this uncommon condition was recognized as early as the first half of the eighteenth century.

ACKNOWLEDGEMENT

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HÆMOLYTIC ANÆMIA IN ACUTE GLOMERULONEPHRITIS[1]

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ANÆMIA has long been known to be of frequent occurrence in nephritis irrespective of the ætiology (Parsons and Ekola-Strolberg, 1933). Its diagnostic value and prognostic significance have been emphasized in glomerulonephritis by many writers. There seems to be little doubt that the severity of the anæmia tends to be directly proportional to the duration and degree of azotæmia. These observations may well be accepted as factual.

The aspect of the anæmia in nephritis requiring close scrutiny is the mechanism of its production and here most of the literature deals with chronic renal disease.

The commonest causes cited are "toxic" depression of bone marrow activity or disturbance of maturation brought about by some unknown and as yet undemonstrated metabolite (Brown and Roth, 1922). An additional observation alleged to be in favour of such hypotheses is the refractory state of the bone marrow to ordinary marrow stimulants. While it is still possible that such theories are correct, there is no direct supportive evidence, and they have come into being mainly through analogy and by exclusion. There are considerable data that this state of affairs does not pertain. The "toxic" metabolite has escaped detection and it is not possible to produce any similar picture by use of any known chemical. Hæmatological findings are also frequently inconsistent, for numerous reports exist in which reticulocytes and even nucleated red cells are described in the peripheral blood of patients with the anæmia of nephritis. In addition the bone marrows from patients with this manifestation of nephritis are often hyperplastic, particularly in erythropoiesis. Emphasizing these discrepancies between the proposed ætiology and the laboratory findings, Emerson in 1949 carefully studied a single case of a white male soldier with a classical first attack of glomerulonephritis. When first seen, this patient had a history of pharyngitis occurring two months previously and an intervening period of increasing weakness and fatigability. Swelling of his legs and an increase in his general symptoms began two weeks prior to his admission to hospital. He had a normocytic normochromic anæmia, his circulating red cell mass was 45% relative to the expected normal for his age, size and sex, and while he was under observation his anæmia became worse.

Emerson studied this patient by carrying out estimations of blood volume and total circulating red cell masses. Using transfusions of Group O blood and cells (the patient's group being A) and differential agglutination red cell counts employing a modification of Ashby's technique, he determined the survival *in vivo* of the two types of cells circulating.

There were two series of transfusions in the experiment, and in the first, Group O whole blood was used and in the second washed red cells from Group O blood resuspended in saline were injected. There was a mild hæmolytic reaction to the first transfusion, apparently due to the presence of iso-agglutinins, but this did not complicate the second transfusion series. His patient showed a significant reticulocyte count, the donor's cells were eliminated at a rate of 3·3% per day, which is three times the expected normal rate, and the removal of the patient's cells was abnormal, being 1·6% per day in spite of the fact that this coincided with an increase in reticulocytes. It is of interest to note than in Emerson's patient, the highest reticulocyte response occurred when the nitrogenous retention was maximal if not marked.

In addition Emerson observed that when the patient was first seen two months after the clinical onset of the nephritis his hæmatocrit reading was 36·7% and two weeks later 30·8%, representing a reduction of approximately 20% and 30% of normal respectively. At the time of the second reading the red cell mass was 45% of the normal, indicating that the anæmia was more severe than appeared from a study of the hæmatocrit reading. This was because the plasma volume was normal. It is not possible to explain these findings on the basis of toxic inhibition of the bone marrow, metabolic defect

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[2] Medical Board Fellow in Medicine.

or nutritional deficiency, unless it is postulated that marrow activity ceased with the pharyngitis two months previously and the destruction of the patient's red blood cells was twice the normal of 0·8% to 1% per day. Against this possibility he points out that if this occurred his original hæmatocrit reading was inaccurate.

The signs of blood destruction were maximal when the blood urea nitrogen content was at its peak and had ceased, and erythropoiesis was apparently normal when the blood urea nitrogen content was declining towards a normal level. This strengthens the view that the degree of anæmia is directly proportionate to the degree of renal impairment. Emerson has therefore presented us with laboratory evidence of excessive blood destruction in a case of acute glomerulonephritis. The role hæmolysis plays in the ordinary case of acute glomerulonephritis still remains unknown, but three cases of nephritis confirmed at autopsy are presented in which the diagnosis of acute hæmolytic anæmia can be entertained.

CASE HISTORIES

Case I

The patient (P.6023, Royal Prince Alfred Hospital) was a three and a half year old female who had been an apparently normal, full-term infant. Her brother and her mother's brother had had neonatal jaundice. Her mother and father were alive and in good health, but her mother's sister had suffered from jaundice for two weeks some twelve years previously. In March of 1950, the child had apparently uncomplicated measles. In October, a sutured laceration of the leg became infected and she was given sulphonamides (7·5 grammes). After she had been one week on sulphonamides, her face became swollen and she developed an urticarial rash which responded to "Benadryl". On November 25 she vomited and it was questioned whether blood was present in the vomitus or not and she continued vomiting throughout the day. Two days later she became oliguric and passed dark red urine. She was given sulphaguanidine, but continued to vomit, and the following day she was noted to be jaundiced, restless, distressed and mentally confused. Her urine continued to be scanty and dark and she was admitted to another hospital on November 28, 1950. On her admission there was some evidence of dehydration. Her liver and spleen were not palpable, but there was a generalized icteric tinge to the skin. Her tonsils were enlarged and reddened and her urine was "solid" with albumin and contained large numbers of red cells. The dark colour of the urine was at one stage attributed to hæmoglobinuria. Her treatment consisted at various times of penicillin, alkalis and, on the twenty-fourth hospital day, chloramphenicol was given in doses of 250 milligrammes every five hours. Fluids were administered by the parenteral route and she was given a blood transfusion on five occasions. Her urinary output throughout observation varied from 120 to 180 millilitres per day, albumin in her urine from "one-eighth" to "two-thirds", red cells were always present in significant numbers and were occasionally profuse. Her blood urea content was 184 milligrammes *per centum*. With catheterization of the bladder pus cells made their appearance in increasing numbers. The child came under the care of the Clinical Research Unit on the twenty-seventh hospital day, when she was observed to be pale, icteric with inelastic skin and a palpable spleen. Her blood pressure was then 110 millimetres of mercury systolic and 60 millimetres diastolic. The child's course throughout was characterized by vomiting, constipation, oliguria and hæmaturia, and she continued in this condition under our care and died on the thirty-fourth hospital day in coma after fibrillary twitchings of muscles of her arms and legs and a series of clonic and tonic fits.

The hæmatological data of this patient are presented in part on the accompanying graph (Figure I).

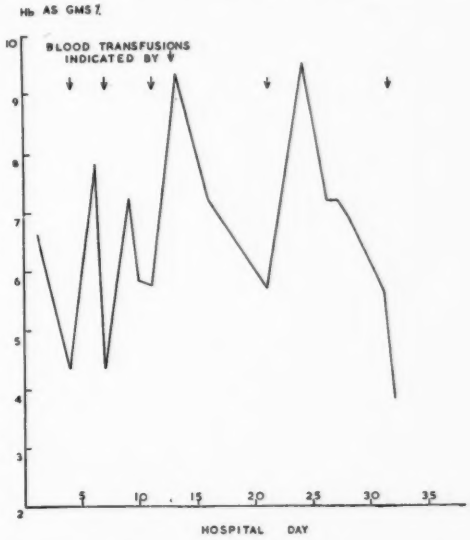

FIGURE I

Chart showing the behaviour of the hæmoglobin concentration and its relation to the blood transfusions

It should be noted that this child of three and a half years received 2,350 millilitres of whole blood in thirty-four days, yet never at any time did her hæmoglobin content rise above 9·5 grammes *per centum*.

In addition to the findings shown on the graph, she had a reticulocyte count of 9,000 per cubic millimetre on the twenty-fourth hospital day and 84,000 per cubic millimetre on the twenty-eighth hospital day. Early in the course of the disease reticulocytes were stated to be numerous and nucleated red cells were frequently seen in the peripheral blood.

Autopsy Findings.—The spleen (40 grammes) was enlarged, but firm in consistency, and there was a small accessory spleen one centimetre in diameter. Both kidneys were enlarged and congested (right kidney 75 grammes, left kidney 85 grammes).

Histological Examination.—In the kidney many of the glomeruli were intensely congested, other glomeruli were bloodless and in some of these there were degenerative foci with an increased number of polymorphonuclear cells in the tuft. An occasional glomerulus had an epithelial crescent. Granular casts were seen in some large tubules. The appearances

were those of a resolving acute glomerulonephritis of the hæmorrhagic type.

The spleen was somewhat congested and numerous phagocytic cells contained pigment and some contained red blood cells. The appearances were consistent with hæmolytic anæmia. There was cloudy swelling of the parenchymal cells of the liver and the Kupffer cells were prominent and contained blood pigment, and some contained red blood cells. The bone marrow was hyperplastic and there was an excess of erythropoiesis over granulopoiesis.

Post-Mortem Diagnosis.—The post-mortem diagnosis was acute glomerulonephritis, probably in a stage of resolution.

Case II

The patient (11.936, Royal Prince Alfred Hospital) was a nineteen year old male with a non-contributory past and family history. His present illness began with an attack of " arthritis " characterized by swelling and pain in the joints of his fingers, elbows, knees and ankles some five weeks prior to his admission to hospital. The swelling and pain disappeared, so that none was demonstrable on his admission to hospital. About a week after the initial stages of this arthritis he began to notice breathlessness and palpitation. He became weak and giddy and developed a cough with some greyish sputum. At the same time he noticed pain in his chest. This was far down on the left side and accompanied by a dragging feeling. Over this whole period he was getting paler and anorexia was becoming a more prominent feature. He was given a blood transfusion one week before coming to the Royal Prince Alfred Hospital and had felt somewhat better since. There were no complaints which could at this time be attributed to the urinary system.

On physical examination he was noted to be a pale, confused youth with slight lymphadenopathy in the axillæ and groins. Blood pressure was 130 millimetres of mercury systolic and 60 millimetres diastolic. On examination of the heart there was an aortic systolic murmur and a triple rhythm was heard at the mitral area. No œdema was detected, but there were flame-shaped and linear hæmorrhages in the ocular fundi. The liver was questionably palpable 1·0 centimetre below the right costal margin at full inspiration, and although the patient had tenderness over the splenic area, the spleen was not palpable. Ward examination of the urine disclosed a specific gravity of 1010, the urine was solid on boiling and chemical tests for blood gave strongly positive results. In the light of this last finding the patient was questioned again and he stated that he thought that his urine might have been dark for the five weeks of his illness prior to his admission.

He was gravely anæmic and the course of his illness in hospital was characterized by repeated transfusions of large quantities of whole blood and packed cells. There was never a stage when his hæmoglobin was maintained at a satisfactory level for more than a few days, in spite of cortisone, which was introduced on the twenty-second hospital day and replaced by ACTH on the twenty-fifth day. His urinary output was poor and proteinuria and microscopic hæmaturia continued throughout.

The patient was classified in Group O, as Rh-positive, R_1, anti-C-positive, and the Coombs test gave indirect negative and direct positive results. The following serological examinations were carried out: Widal test gave no reaction against *B. typhosus*, O and H; *B. paratyphosus* A, O and H; *B. paratyphosus* B and C; *B. proteus* O × 19; and *B. abortus*. The Widal test gave a positive reaction against *B. proteus* O × K, 1/25. The result of the Paul Bunnell test was negative in all dilutions and the result of the Wassermann test was negative. The patient repeatedly complained of pain in the left hypochondrium and his spleen eventually became palpable. By the twenty-ninth day, that is four days after administration of ACTH had been commenced, he had marked peripheral œdema and established ascites while his blood pressure had risen precipitously to 165 millimetres of mercury systolic and 90 millimetres diastolic. He had several

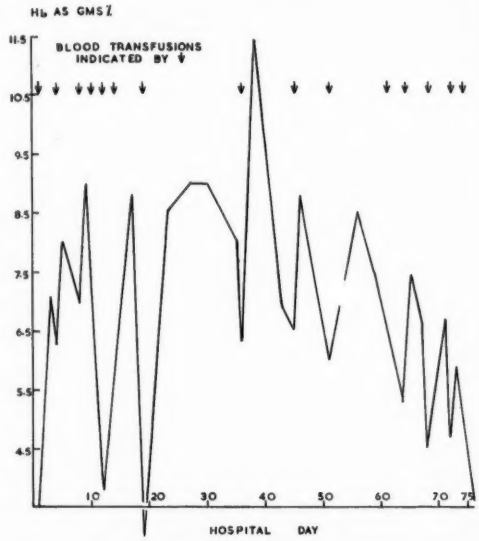

FIGURE II

Chart showing the behaviour of the hæmoglobin concentration and its relation to the blood transfusions

paracenteses abdominis with the removal of pale ascitic fluid. By the thirty-sixth day his blood pressure was 200 millimetres of mercury systolic and 115 millimetres diastolic, and proteinuria and microscopic hæmaturia were marked. Clinical examination of his heart indicated that its size was increasing. Between the thirty-ninth and forty-first hospital days he had seven major epileptiform fits and his cerebro-spinal fluid pressure was recorded as being 300 millimetres of water with the patient at rest and at ease. ACTH administration was suspended and only token courses were given during the remainder of the patient's life. Oliguria became more marked, œdema and ascites increased and hypertension with a blood pressure of 170 millimetres of mercury systolic and 110 millimetres diastolic to 200 and 160 millimetres of mercury persisted. Between the forty-ninth day when his proteinuria was reported as being " three-quarters " and the seventy-sixth day, when the patient died, he had further transfusions, fluctuating icterus, oliguria and increasing fluid retention. His death was caused by pulmonary œdema.

The state of the patient's red blood cell series is shown in the accompanying graph depicting the changes in his peripheral blood hæmoglobin concentration (Figure II).

The anæmia was normocytic and normochromic, the mean corpuscular volume was 90 cubic microns, the mean corpuscular hæmoglobin content was 30 micromicrogrammes, and the mean corpuscular hæmoglobin concentration was 33%. During the early stages of his disease nucleated red blood cells, neutrophile myelocytes, premyelocytes and occasionally as many as 860 unclassifiable cells per cubic millimetre were seen in the peripheral blood. His polymorphonuclear leucocytes showed a shift to the left, while the platelets were essentially normal. Osmotic fragility of his red cells was normal compared with a normal control. The total serum bilirubin content was 0·4 milligramme *per centum* on the fourth day, but had risen to 2·5 milligrammes *per centum* on the fifteenth day. Reticulocytes were a feature throughout the illness, the highest reading being 20% of a total red cell count of 2·09 millions on the thirty-sixth day.

As this patient's severe hæmolytic process overshadowed his whole clinical picture, there are unfortunately no records of the degree of nitrogen retention.

Autopsy Findings.—The heart was enlarged and dilated, weighing 570 grammes, and the tricuspid valve admitted six fingers and the mitral four. The spleen weighed 995 grammes and was grossly enlarged. There was some early fibrous perisplenitis. Both kidneys were larger than normal (250 and 266 grammes). The capsule stripped easily and the surface was smooth with numerous subcapsular hæmorrhages.

Histological Examination.—In the kidneys the appearances were those of a subacute diffuse glomerulonephritis. The lesions in the glomeruli were all of different ages and the most advanced showed complete fibrosis of the glomeruli. The lesions could have conceivably dated back to the commencement of the illness. There was a good deal of pigment (siderosis) in the Kupffer cells of the liver and the spleen was packed with red cells, there being evidence of blood destruction, namely pigmentation and erythrophagocytosis. The bone marrow was very active and erythropoiesis dominated the picture.

Post-Mortem Diagnosis.—The post-mortem diagnosis was subacute diffuse glomerulonephritis.

Case III

The final case is that of an eight months old male child whose previous health had been quite normal, apart from intermittent attacks of vomiting. His illness appears to have begun when he refused his feeds and had diarrhœa (five to six motions per day). He was given parenteral therapy and sulphadiazine. On the fourth day of the illness he had a convulsion and after this was very drowsy and was brought to the Royal Alexandra Hospital for Children, where it was found that he had been oliguric for the preceding twenty-four hours. On admission he was described as a pale, moribund infant twitching intermittently. The original provisional diagnosis was septicæmia and he was given fluids parenterally and intensive antibiotic therapy including sulphadiazine. Pallor was marked and there were a few petechiæ which appeared over the abdomen and legs. He had congested fauces. Fluid replacement therapy was continued without the production of any urine and he was given 240 millilitres of whole blood on the fifth day of his illness. His weight was increasing, his blood pressure was 115 millimetres of mercury systolic and 75 millimetres diastolic, and his liver became palpable. He was not noticeably jaundiced and on the eighth day, after a further transfusion of 120 millilitres of whole blood, his condition became rapidly worse and he died.

His blood urea content was 280 milligrammes *per centum* on the seventh day and 320 milligrammes on the following day. His serum bilirubin content estimated on the seventh day was reported as being within normal limits. Ward examination of the urine revealed "solid" albumin and microscopic examination, profuse red cells and granular casts. Pus cells and red cells were seen in the stool. His hæmoglobin content on his admission to hospital was 5·0 grammes *per centum*; the next day, after he had received 240 millilitres of blood, it was 6·0 grammes *per centum*, and had risen to 7·2 grammes *per centum* on the day of his death. He had a leucocytosis with an absolute increase to 4000 to 8000 neutrophile cells per cubic millimetre. Thrombocytopenia was present of the order of 30,000 to 45,000 cells per cubic millimetre.

Autopsy Findings.—The lungs were congested and very œdematous with frothy fluid in the main bronchi. The liver was moderately large, but presented no grossly abnormal features. The alimentary tract was normal and showed no ulceration. Macroscopically the kidneys were both enlarged and bulged from the split capsule which was not adherent. Their surfaces were smooth and congested with numerous pin-point hæmorrhages, while the cut surface showed marked congestion with hæmorrhages in the medulla, but no disturbance of normal architecture. The bladder was empty at post-mortem examination.

Histological Examination. — The glomeruli were severely involved in an acute necrotizing inflammatory process, and while many of the afferent arterioles were similarly involved, the vasculature was otherwise unaffected. Severe degenerative changes were seen in the tubular epithelium and many tubules were filled with blood and colloid casts. The interstitial tissue was œdematous. In the bone marrow there was abundant hæmopoietic tissue including megakaryocytes, with some excess of erythropoietic over leucopoietic elements.

Post-Mortem Diagnosis.—The post-mortem diagnosis was acute necrotizing glomerulonephritis and pulmonary œdema.

DISCUSSION

Three cases of nephritis have been presented. Two of these were acute, and one was subacute, glomerulonephritis. They all present certain common features worthy of note. Firstly, the degree of anæmia was marked, secondly hypertension was absent at least when the patients were first seen, and thirdly all were fatal in their outcome. An additional characteristic is that all three patients had hyperplastic bone marrows at post-mortem examination.

In none of these cases does blood loss appear to have been a factor, for the hæmaturia was always microscopic and in Case II only blood-streaked vomitus was seen and a slightly positive occult blood in fæces on one occasion.

These cases are unusual in that there was a severe grade of anæmia. The anæmia of acute

nephritis is characteristically described as mild, but in the light of the work of Harris and Gibson (1939) the anæmia in any case of acute nephritis may be greater than is apparent by examination of hæmatocrit, hæmoglobin and red cell count. This is because the plasma volume is normal and the total blood volume reduced.

In Case I the evidence for a hæmolytic mechanism in the production of the anæmia seems fairly definite, in spite of the fact that a Coombs test was not carried out. The child was jaundiced at the onset and continued to show this sign through her illness. Hepatic disease was not present. Five separate transfusions totalling almost 2·5 litres of blood were insufficient to maintain the hæmoglobin value of this three and a half years old child during her thirty-four days' illness. Furthermore, reticulocytes were described as being numerous early in the disease and later a count of 3% in a total red cell count of 2·8 million was obtained. Nucleated red blood cells were frequently seen during the first week. While hæmoglobinuria was stated to have occurred, this was a single observation and there was no post-mortem evidence to support the contention that intravascular hæmolysis had occurred. There can be no doubt that this child had acute nephritis and all the available data point to hæmolysis as the cause of her anæmia. It is also suggested that the destruction of red blood cells occurred outside the vascular compartment and that this hæmolytic anæmia belongs to the group in which the red cell is destroyed predominantly in the reticulo-endothelial system.

In Case II attention was directed to the hæmolytic anæmia during life although severe albuminuria and oliguria existed together with hæmaturia of a microscopic degree. Though initially normotensive, this patient rapidly reacted adversely to ACTH which in fourteen days produced what could be described as hypertensive encephalopathy. It would seem fairly certain that this gross response to ACTH was actuated by the presence of nephritis. His hypertension, once initiated, never abated and signs of renal damage continued side by side with a florid hæmolytic anæmia. This patient had a directly positive result to the Coombs test and abundant collateral evidence of a hæmolytic process.

Even without the niceties of Emerson's study, it is considered that both these cases represent examples of anæmia in nephritis in which the mechanism of production of the anæmia was a hæmolytic one.

The final case is presented as being suggestive. As far as can be determined this infant's illness began four days before his admission to hospital and he had been well apart from intermittent attacks of vomiting. If this premise is allowed, then the hæmoglobin content at the time of admission of 5·0 grammes *per centum* can most readily be explained on the basis of excessive red cell destruction. The single bilirubin determination on the seventh day of the illness was expressed as normal, but as a counter to this objection we may cite the example of Case II, in which the bilirubin content was 0·4 milligramme *per centum* on the fourth hospital day and also that the infant's bone marrow when examined at autopsy was hyperplastic with erythropoiesis in excess of leucopoiesis. Unfortunately no reticulocyte count was made. It is reasonable to postulate that a hæmolytic process was present in this case of fulminating acute nephritis.

Hæmolytic anæmia is known to occur in a variety of conditions, and as a manifestation of diseases such as acute disseminated *lupus erythematosus* or chronic leuchæmia, may be a fairly non-specific accompaniment. Hæmolytic anæmia such as has been reported here and by Emerson occurring in nephritis may bear the same relationship to the parent disease as it does in an infectious disease, for example, infectious hepatitis.

Most, if not all, cases of acquired hæmolytic anæmia are dependent upon the presence of complete or incomplete antibodies in the plasma of the subject. These antibodies sensitize the red cells so that, either singly or in clusters, they are susceptible to destruction in the reticulo-endothelial system and so extravascular hæmolysis occurs. Naturally the greatest evidence of this destruction is found in the spleen, but the whole of the reticulo-endothelial system participates in the destructive process. In anæmias of this type a positive result to the Coombs test is obtained, and the antigen in the vast majority of instances is unknown.

Acute nephritis is thought on fairly good grounds to be a tissue response to an antigen-antibody reaction. It may be that the accompanying hæmolytic anæmia is due to a sensitization of the red cell by antibodies in a similar fashion to that just described as occurring in the acute acquired hæmolytic anæmias.

If it is indeed a fact that there is some relation between the antigen-antibody reaction leading to the nephritis and to the hæmolytic anæmia, then two possibilities are suggested. Firstly, the antibodies causing the nephritis also sensitize the red cell, and secondly, the causative agent

of the nephritis, for example the hæmolytic streptococcus, is capable of producing at least two distinct antigens under appropriate circumstances. One leads to the well-known antigen-antibody reaction culminating in nephritis, while the other leads to the formation of separate antibodies which sensitize the red cell and so induce a hæmolytic anæmia. In either case one would expect to find a positive direct result to the Coombs test. This certainly applied in the case of the young male (Case II), and one can declare with a certain amount of assurance that in Case I the hæmolysis was at least extravascular. All the available evidence in these two cases and in Emerson's patient points to the presence of a hæmolytic anæmia of the type in which destruction of the red cell occurs outside the vascular compartment in the reticulo-endothelial system. It follows then that they belong to the same category as the acquired hæmolytic anæmias as opposed to hæmolytic anæmias resulting from intravascular hæmolysis.

SUMMARY

Two cases of glomerulonephritis are presented, one acute and the other subacute, in which severe anæmia was brought about by a hæmolytic mechanism. A third case of nephritis with evidence suggestive of a hæmolytic anæmia is reported.

Prominent autopsy features were hyperplastic bone marrows affecting erythropoiesis in excess of leucopoiesis, evidence of increased blood destruction and an absence of findings in the kidneys suggesting intravascular hæmolysis or " lower nephron nephrosis ".

A possible ætiological relationship between the glomerulonephritis and the accompanying acquired hæmolytic anæmia is discussed.

ACKNOWLEDGEMENTS

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HYDATID DISEASE OF THE PERICARDIUM[1]

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While it is recognized that the heart and pericardium are less commonly infested than some other viscera, hydatid disease of this region presents many unique problems as yet unsolved. A consideration of the pathology will show features not seen in hydatid disease elsewhere in the body. An instructive case is reported here, showing many features typical of this disease.

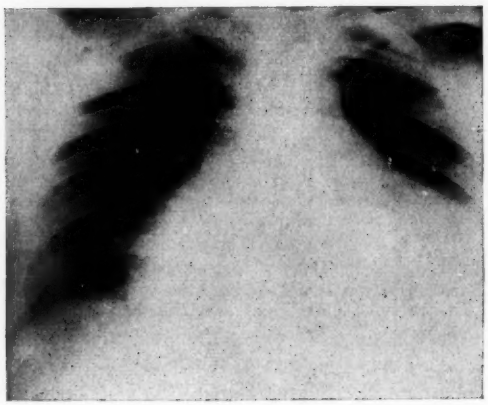

Figure I
Radiograph of the chest showing great increase in the heart shadow. Pulsation was much diminished. Pericardial effusion was diagnosed. (February 1940)

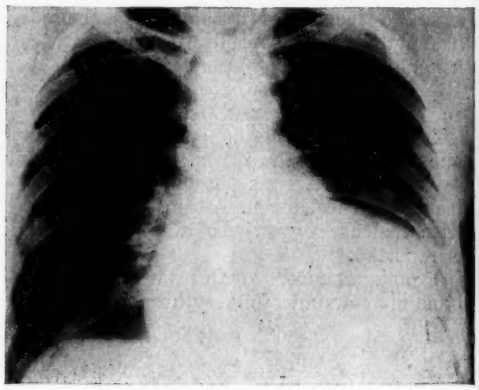

Figure II
Radiograph showing some decrease in the size of the heart shadow during two months (compare Figure I). There is still some pericardial effusion. (April 1940)

Case Report

G.B. was a man, aged thirty-one years, when he died in May 1948. He had enjoyed good health until February 1940, when he was admitted to hospital complaining of pain in the left side of his chest. This pain had begun in the epigastrium five days previously and shifted upwards into the left chest, going through to the back on that side and into the left axilla. A dry cough followed this pain and seemed to make it worse. His temperature was 39·7° C., his pulse rate 110 per minute, and the systolic blood pressure was 110 and the diastolic pressure 70 millimetres of mercury. Physical examination of his chest showed that movement of the left side was impaired and the signs of a left basal pneumonia were present. The apex beat was impalpable. No abnormal heart sound was heard. He was treated as though he was suffering from pneumonia. Two days later he was slightly cyanosed and a harsh pericardial friction rub was present, maximal at the base of the heart. The heart sounds were fainter. The area of dulness to percussion and tubular breathing now extended up to the sixth rib posteriorly. The diagnosis of pericarditis with effusion was confirmed radiologically (Figure I) and aspiration was attempted. Five millilitres of cloudy fluid were obtained which microscopically contained only blood and yielded no organisms on culture. Over the next month his temperature slowly returned to normal and the signs in his chest slowly cleared. Two months after his admission to hospital radiological evidence of a small pericardial effusion was still present (Figure II). He was discharged afebrile and free of symptoms. The pericarditis was regarded as probably secondary to his left basal pneumonia.

For six years he was well.

In 1945 he developed a right pleural effusion which cleared after two months' rest in bed. This was suspected to be due to tuberculosis, but no organism was identified.

In 1946 brisk hæmoptysis occurred, yielding over one pint of bright blood, after which he had six further hæmoptyses. A persistent cough appeared with a fair amount of sputum, usually streaked with blood.

In the six months before his death he had noticed "grape skins" in his sputum on several occasions. Once, this had been accompanied by swelling of his face and neck, with generalized itching of the skin which subsided in a few days. His exercise tolerance during this period was normal and he continued his strenuous occupation as a labourer.

[1] Received for publication on July 18, 1952.

He was admitted to hospital in April 1948, after a prolonged hæmoptysis of nearly two pints of blood. His temperature was 38·3° C., his pulse rate 130 per minute and his systolic blood pressure was 130 and his diastolic pressure 60 millimetres of mercury.

On examination of his chest, the lower left ribs were more prominent anteriorly and there were signs of pneumonia over the right mid-zone posteriorly. The apex beat was forcible, but not displaced. A systolic bruit was audible at all areas, maximal over the pulmonary valve area. Copious offensive purulent sputum, often blood-stained, was produced, and a lung abscess was suspected. Radiological examination of the chest (Figure III) revealed several circular shadows near the periphery of both lung fields and an area of opacity in the right mid-zone with a fluid

FIGURE III

Radiograph showing some residual enlargement of the heart shadow. Several rounded opacities are present in the peripheral lung fields, most easily seen in the right lower lobe, the left upper lobe and just behind the apex of the heart. An area of diffuse opacity is present in the lower part of the right upper lobe, with a fluid level near its upper border; this was the site of the infected hydatid cyst. (February 1948)

level discernible near its upper limit. The diagnosis was considered to be multiple pulmonary hydatid cysts, with suppuration in a cyst of the right upper lobe leading to a lung abscess. The heart shadow was increased in width and the fullness of its upper border suggested that the source of the pulmonary hydatid cysts was to be found in the pericardium.

Culture of the sputum yielded *Staphylococcus aureus*, coagulase positive. Postural drainage and chemotherapy combined to improve his condition until he was afebrile, but still producing small amounts of purulent sputum. Fragments of hydatid membrane were present in the sputum at times.

When further improvement appeared unlikely to occur, the infected hydatid cyst was drained transpleurally by resection of part of the right fourth rib after radiological localization (Figure IV).

Two weeks later, when afebrile and sitting out of bed, the patient had a sudden drenching hæmoptysis. Blood flowed from his nose and mouth and within one minute he was cyanosed and unconscious. Laryngoscopy and bronchoscopy were performed

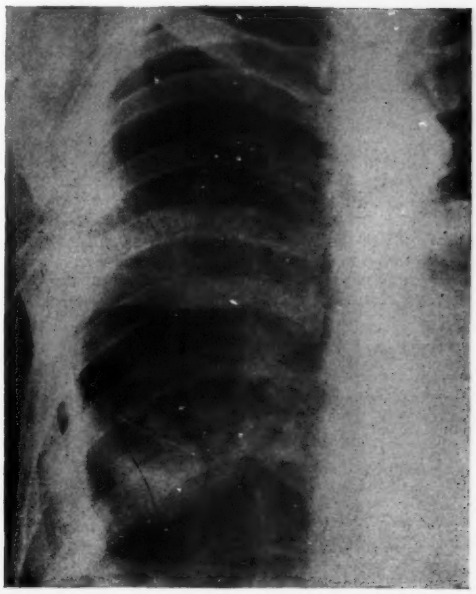

FIGURE IV

Post-operative radiograph showing some clearing of the right upper lobe opacity. The rounded shadow in the right lower lobe is easily seen. (March 1948)

immediately, with the removal of much fluid blood and clots, but without avail. The pulse had ceased within three minutes of the hæmorrhage.

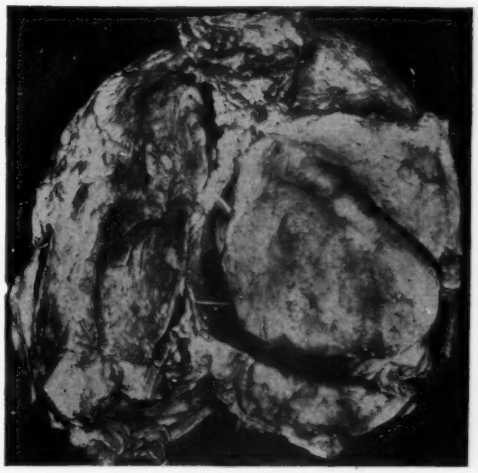

FIGURE V

Photograph of the thoracic viscera. The thickened and adherent anterior wall of the pericardial sac has been reflected to show the subepicardial situation of the hydatid mass. This mass overlies the upper borders of both ventricles and extends to the great vessels. The pleura over the right lung is thickened

At autopsy the pericardial sac was slightly thickened at all points, but especially over the apex of the left ventricle where it was adherent to the subjacent tissue. A mass of hydatid tissue occupied a large part of the pericardial space (Figure V), displacing the heart to the right. The hydatid was composed of several laminæ of pale, gelatinous tissue with intervening areas of homogeneous yellow material. This mass extended upwards beneath the epicardium from the apex over the anterior and left surfaces of the heart and had penetrated the pulmonary artery. The hydatid membrane projected into the lumen of the pulmonary artery without any covering layer (Figures VI and VII).

The myocardium underlying the hydatid mass appeared normal and without scar. The heart cavities and endocardium were normal.

There was no evidence of hydatid cyst formation elsewhere in the body.

DISCUSSION

This case illustrates many of the features typical of hydatid disease of the heart, in that it allows an accurate correlation of the clinical history with the autopsy findings and it provides histological evidence of the fate of hydatid emboli in the lungs.

The first typical feature worthy of comment is that the heart was the sole organ involved in the primary hydatid infestation in this patient.

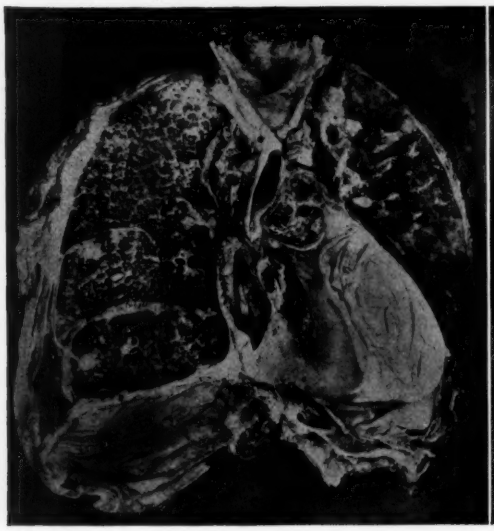

FIGURE VI
Photograph of the thoracic viscera sectioned in the coronal plane. The laminated, collapsed hydatid mass is seen displacing the heart and eroding the wall of the pulmonary trunk. Small hydatid cysts are present in both lungs, that in the inner part of the left upper lobe being the source of the fatal hæmorrhage

FIGURE VII
Photograph of a more posterior section (compare Figure VI) showing the unprotected mass of hydatid tissue projecting freely into the lumen of the pulmonary trunk. The remains of the infected hydatid cyst which has been drained is seen in the right upper lobe. A small post-operative hæmothorax is present

The pleura was thickened over the right lung and some old clotted blood was present in the pleural sac from the thoracotomy on that side. A large number of small hydatid cysts were scattered throughout both lungs. These possessed thin adventitial coats and in some parts had followed the course of the bronchial passages. In the lower part of the right upper lobe was an area of firm tissue underlying the area of greatest pleural thickening. This contained the thick-walled hydatid cyst which had been drained surgically (Figure VII).

Several cysts up to three centimetres in diameter were scattered in the periphery of both lungs. One of these in the left upper lobe contained recent blood clot and partly disintegrated hydatid membrane (Figure VI). This appeared to have been the source of the fatal hæmorrhage. Hydatid membrane fragments extended into right and left pulmonary arteries and emboli were present in the intrapulmonary branches.

In a series of 137 cases of cardiac hydatid disease from the literature reviewed by Dévé (1928), the heart was the only organ involved in 82%. This is an important fact when considering the mode of infection.

A distinction is usually made between "primary" hydatid disease in which the heart alone is involved, and "secondary" hydatid disease when spread to the heart appears to have followed rupture of another cyst elsewhere in the body, for example, liver or lung.

Cases of myocardial hydatid disease in animals show the same solitary nature of the cyst in the heart as in those cases in the cow reported by Rahimuddin (1943), Gallo (1934), Gagliardi (1935) and Köpps (1937) and in the buffalo

reported by Magsood (1944). In the case of Bocci (1934) the hydatid cysts present in the kidney of the cow were almost certainly secondary to the cardiac cysts present.

The solitary nature of the hydatid infestation of the heart in most cases both in man and beast may mean one of two things. Either the heart is the first organ in the body to become infected and no other focus of infection is established, or the heart infection is secondary to an infection elsewhere in the body which has retrogressed. The possibility of retrogression of the primary cyst in over 80% of these cases is unlikely since it must have grown large enough to have ruptured into a blood vessel and in that time, sufficient adventitial fibrosis would have occurred to leave some permanent evidence of its existence. In those cases in which cysts are present elsewhere in the body it may be argued that the heart cyst is secondary to these. The distribution in 80 cases quoted by Dumont (1918) was 64% in the brain, 17% in kidney and 17% in the spleen. While it is not impossible that some of these peripheral cysts were primary, or that some other primary cyst, possibly in the liver, was overlooked, it is most likely that in all cases they were secondary, arising by embolism from the cardiac cyst.

There are two routes by which the hexacanth embryo may reach the myocardium—by the coronary arteries and by direct penetration of the lining of heart cavities. In attempting to account for the peculiar solitary nature of cardiac cysts, Kelly (1869) suggested that infection in these patients had occurred in the region of the fauces, allowing transport of the embryo to the heart without its entering the liver and that then direct implantation in the right auricle had taken place. A much more recent theory embracing the same doctrine as Kelly's has been put forward by Jorge and Re (1946), that there is an alternate route for the hexacanth embryo passing from the alimentary canal to the heart. These workers point out that the embryos may enter the lymphatics from the gut and pass up the thoracic duct to enter the right atrium from the great veins. In this way the liver is by-passed. The embryos are introduced into the heart cavities and may pass directly through the endocardium or penetrate the Thebesian veins. This mechanism would be consistent with a higher incidence of infection on the right side of the heart, but the figures of Dévé (1928) have indicated that this is not so (see Table I).

While it is possible that in some cases primary hydatid disease of the heart is acquired by this direct route, the distribution of the cysts in the myocardium as shown in the above Table I makes it clear that the coronary arterial tree is the main channel by which the embryos reach the myocardium. The long route taken to reach the coronary vessels is the most remarkable feature. The embryos almost certainly are ingested and pass from the lumen of the foregut to the liver in the portal blood stream, then through the liver sinusoids to the right side of the heart, next through the lung capillaries to the left side of the heart and finally they

TABLE I
Showing the Distribution of Hydatid Cysts in 110 Cases

Situation.	Number of Cases.	Atrium.	Ventricle.
Left side of heart ..	56	8	48
Right side of heart ..	36	11	25
Septum	18	3	15

enter the orifice of a coronary artery. This last part of the route must be very precarious, depending on eddy currents carrying the embryos out of the central stream at the aortic valves; entrance to the coronary artery then probably coincides with the phase of maximum flow in mid-diastole (Gregg *et alii*, 1935), being facilitated by the aortic valve cusps, which are closed at this stage. Dévé (1917) has estimated that, of the embryos entering the portal circulation, 75% are filtered out in the hepatic sinusoids and 8·5% in the lung sinusoids, which are of larger calibre. In other words only a small proportion of embryos ingested will ever reach the left side of the heart, and very few of these are carried into the coronary circulation. This is consistent with the low incidence of cardiac hydatid disease which must lie between the estimations of 1·95% by Thomas (1894) and 0·5% by Dévé (1917).

The mechanism for the production of solitary primary heart cysts without liver or lung infection, particularly if the by-pass along the thoracic duct route is not accepted, is obscure. It is possible that the constantly recurring pressure changes to which myocardial hydatid cysts are subjected may play a part. If, at the time of primary infestation, there were several foci of hydatid emboli established in the body, say in liver or lung as well as in the myocardium, a factor might come into action very early that would prevent growth of these other emboli and lead ultimately to their retrogression and disappearance. Jorge and Re (1946) suggest that the pressure changes in the young myocardial cyst may cause some diffusion of the hydatid fluid into the general circulation, conferring an immunizing action on the body, possibly by the production of antibodies. This

hypothesis has no direct proof in the demonstration of antibodies, but these workers describe with illustrations a case in which small degenerate hydatid cysts were demonstrable beneath the endocardium ; the dense adventitia with eosinophilic leucocytes and prominent vessels around the cardiac cyst are interpreted by these writers as evidence of auto-immunization. Both these phenomena, however, may be interpreted on the basis of the nutritional requirements of the growing cysts.

Other special features in this case are the presence of daughter cysts, the subepicardial location of the hydatid mass after its initial rupture and the phenomenon of erosion of the pulmonary artery with repeated rupture into the blood stream.

It is recognized that daughter cyst production is related to an injurious period in the history of the cyst. The injury may be either chemical or traumatic in nature. The myocardium shares with skeletal muscles the high incidence of daughter cyst formation, this being present in most recorded cases of cardiac hydatid disease. The constantly recurring pressure changes to which cysts in these muscular tissues are subjected must play a large part in causing daughter cyst formation.

The occurrence and frequency of rupture of cardiac hydatid cysts into the pericardial sac need to be stressed because, if a correct diagnosis is made and treatment is carried out, the subsequent almost inevitably fatal rupture back into the cardiac chambers may be prevented. The case reported here illustrates the tragedy of not considering this possibility. Subepicardial rupture has been reported by Dobrotin (1926), but a group of hydatid cysts found at autopsy beneath the epicardium as in the present case does not necessarily mean that the epicardium remained intact at the time of the initial rupture. In many cases cysts have grown on the surface of the epicardium and become covered by a layer of fibrous tissue to give them the appearance of being subepicardial. This encapsulation represents organization of the fibrin coating, by which the freshly ruptured cysts were adherent to the heart wall and were actually part of their adventitia. Figure V shows this appearance of subepicardial localization although it is certain that some years previously there had been free rupture of hydatid elements into the pericardial sac producing the effusion seen in Figure I. The same appearance is seen in the specimens reported by Dobrotin (1926) and Bacaloglu *et alii* (1929). An early report of a primary cyst of the right auricle producing secondary pericardial cysts is that by Baecchi (1909).

In a review of 90 ruptured cardiac hydatid cysts from the literature, Dévé (1928) reports 20 cases of rupture into the pericardium, so that pericardial rupture is less than one-quarter as common as endocardial rupture. The spiral arrangement of the muscles in the heart wall may be an important factor in determining the direction of expansion and rupture of cysts in the myocardium.

The consequences of pericardial rupture may be :

(i) Sudden death due to rupture of the heart at the site of the mother cyst and hæmorrhage into the pericardial sac. This is most likely when a large cyst has ruptured, leaving only a thin inner wall to withstand the pressure within the ventricle.

(ii) Death of the hydatid cyst with slow change to a pultaceous or creamy mass which may resemble old pus.

(iii) Survival of the hydatid elements with daughter cyst formation and a fibrous covering on the epicardial surface of the heart.

(iv) Progressive growth of the pericardial hydatid cysts and rupture back into the heart chambers or the great vessels at the base of the heart, as in the present case.

It is very unusual for pericardial hydatid cysts to perforate the parietal wall of the sac, as shown by the large cyst 9·0 centimetres in diameter reported by Marten (1921) which had not yet done this. The frequency with which inward rupture occurs must be related to the dense fibrous wall of the pericardial sac in man limiting expansion. Dévé (1931), by experimental inoculation of scolices into a rabbit's pericardial sac, produced a large cyst which grossly distended the sac without any cardiac involvement. He explained this result as being due to the thinner pericardium of the rabbit.

When rupture occurs back into the heart chambers, it is usually into the auricles, as in the cases of Foresti and Bonaba (1914) and Dévé and Jirou (1920). This is most likely due to the thinner wall of the auricle and, for the same reason, rupture may occur into the vessels, as in the present case in which the pulmonary artery was penetrated. The consequences of rupture into the pulmonary artery will be similar to those of rupture of myocardial cysts into the right-sided cavities of the heart. Obstruction of branches of the pulmonary artery may produce pulmonary infarction as reported by Hynd (1924), and in several cases

in the literature a history including attacks of pleurisy is given, the patients later dying with established pulmonary cysts.

The patients of Stirling and Allen (1879) and Grulee (1905), like those reported in this paper, presented with hæmoptysis and coughing up of hydatid membranes. In these cases rupture, with spontaneous closure of the defect, must have occurred months or years previously, allowing growth of the implanted hydatid elements to occur until they were large enough to involve and erode the wall of a bronchus.

Repeated rupture, as shown by recent pulmonary artery embolism with daughter cysts in the presence of multiple established lung cysts, had occurred in the case reports of Budd (1859), Stirling and Allen (1879) and Grulee (1905). This phenomenon is also seen in the present case. Sudden death follows rupture when occlusion of the large vascular channels occurs, as in the case reported by Crowther (1880) when the main right pulmonary artery was occluded.

Rupture of a cyst also liberates hydatid fluid and, if fertile, brood capsules and scolices. The release of hydatid fluid directly into the blood stream will usually produce anaphylactic phenomena if there has been any sensitization from a previous small leakage. Anaphylaxis may be so severe that death occurs in the shocked subject, or manifests itself as an urticarial rash, as occurred in the present case, or as a period of bronchospasm.

After rupture, fragments of hydatid membrane from the mother cyst may lodge as peripheral emboli in the same way as the escaping daughter cysts. The fate of these hydatid emboli is of biological importance as representing a method of spread of the infestation. It is clear that some emboli survive and grow to form adult cysts, like the multiple small cysts present throughout both lungs in this case. Some of these growing cysts find their way from the point of initial impaction beside a bronchiole (Figure VIII) into the lumen of the respiratory tract and enlarge in this new position. This accounts for the lining of respiratory epithelium in the adventitia of many pulmonary hydatid cysts. However, considering the enormous number of fertile hydatid elements released into the pulmonary blood stream on rupture of the cyst, it is clear that these have not all survived and grown to form secondary cysts. The fate of these unsuccessful implants is to die and to be surrounded by a tissue layer showing the usual changes of a foreign body reaction, with stromal proliferation, small round cell aggregation and the formation of multinucleated giant cells (Figure IX). Secondary cysts may degenerate at any stage. In some, polymorphonuclear leucocytes are packed about the degenerated hydatid cyst, giving the appearance of a small abscess. The predominance of polymorphonuclear leucocytes is due to secondary pyogenic infection (Figures X and XI).

It is important to recognize that the failure of most hydatid implants to survive is of the greatest prognostic significance to the patient.

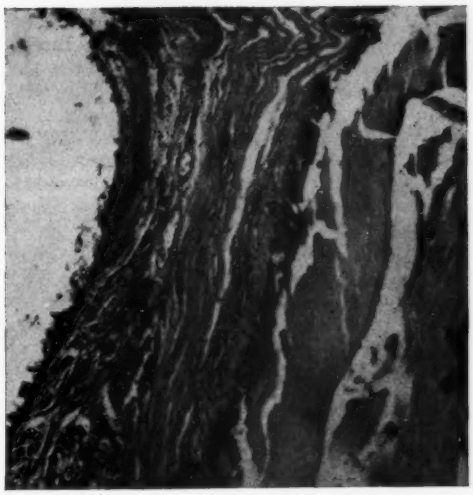

FIGURE VIII
Photomicrograph of a section showing degenerating hydatid cyst in apposition to a small bronchiole. Giant cells are present in the adventitia of the cyst. (× 50)

The same phenomenon of degenerating hydatid emboli surrounded by foreign-body giant cells is seen in the cerebral, renal, splenic and intramyocardial vessels in the case reported by Bacaloglu *et alii* (1929).

The Problem of Diagnosis

A feature of this case is that, had it been diagnosed at the time of the pericardial rupture, surgical therapy might have prevented the tragic series of events which followed.

The attack of pericarditis in a previously healthy young man aroused speculation, but his previous residence in a hydatid district was not correlated with this mysterious pericardial effusion. A Casoni test at this time would have been of great assistance if the result had been positive. Unfortunately the fluid aspirated failed to show hydatid elements and the cause

of the protracted pericardial effusion was not diagnosed.

The heart shadow did not return to normal, but again the possibility of hydatid disease was not suspected until the lung cysts appeared and explained the patient's hæmoptyses. At this stage the diagnosis of hydatid disease of the heart with pericardial and pulmonary spread was clear. The direct invasion of the wall of the pulmonary trunk explained the pulmonary systolic bruit audible during life and appeared to have been present for some time. This is consistent with the evidence of repeated rupture seen in the coexistence of established peripheral lung hydatid cysts with fragments of hydatid membrane and daughter cysts which clearly had only recently lodged in the peripheral branches of the pulmonary artery.

In recent years the diagnosis of cardiac hydatid disease is being made with increasing frequency, mainly because of the increasing use of radiography, but the correlation of all available information is necessary for any diagnosis. A history which includes cardiac symptoms may be given, or there may have been attacks of pleurisy and hæmoptysis. The presence of hydatid membrane in the sputum makes the diagnosis of pulmonary hydatid lesions certain; it is clear that the presence of a primary cardiac cyst should be sought. A past attack of pericarditis is sometimes mentioned and may indicate an episode of pericardial rupture. Finally the history will often reveal previous residence in sheep-rearing districts. Several of these points were present in the case history under discussion.

The physical examination may reveal nothing abnormal, but a bulging of the precordium can be produced by a pericardial cyst of long standing acquired during childhood; there may be an increased area of cardiac dulness, or the friction rub of pericarditis. In the present case a systolic bruit was confined to the pulmonary area and was shown at autopsy to be due to partial obstruction of the pulmonary trunk by hydatid membrane.

Of the special investigations the radiological examination of the heart and lungs with films and screening are the most important. There may be an increase in the size of the heart, as in Figures I and III, which is found on screening not to exhibit the normal degree of pulsation. A discrete rounded shadow may be seen arising from the normal cardiac outline, again exhibiting

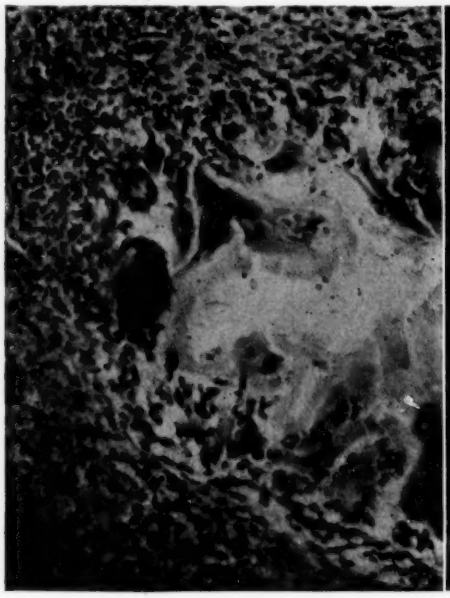

FIGURE IX
Photomicrograph of a section showing multinucleated giant cells in contact with small degenerating hydatid cyst in lung. (× 150)

FIGURE X
Photomicrograph of a section showing two small degenerating hydatid cysts in the lung, surrounded by multinucleated giant cells in a region heavily packed with polymorphonuclear leucocytes. (× 50)

transmitted rather than expansile pulsation, and it was on this finding that Long (1932) made his preoperative diagnosis. The significance of a rounded, calcified shadow in the region of the heart is discussed by Zizmor and Szucs (1945), who agree with Attwood *et alii* (1941) that a hydatid cyst is the most likely diagnosis.

The radiological picture of multiple spherical opacities of roughly similar size distributed in the periphery of one or both lung fields

FIGURE XI
Photomicrograph of a section showing degenerating hydatid cyst lying in a small abscess cavity packed with polymorphonuclear leucocytes and surrounded by granulation tissue. (× 50)

arouses at once the possibility that a hydatid cyst may have ruptured into the right side of the heart or pulmonary trunk, and diffuse sowing of germinative hydatid elements through the lungs occurred. This phenomenon assisted in the diagnosis of the present case.

Serological diagnosis is not always accurate, for the Casoni test may yield a negative result as in the case of Attwood *et alii* (1941). A positive complement fixation reaction is unlikely to be found if the cyst is dead or if leakage of cyst fluid has not occurred within the past year or two. However, a positive result to a test of either kind, taken in conjunction with a suspicious history or shadow, should be regarded as strong confirmatory evidence.

The electrocardiogram may show changes consistent with myocardial damage of non-specific type and so is found in a young person who has this disease. Eosinophilia is sometimes present, but it is not to be expected in older degenerate cysts and forms only a small part of the evidence upon which a diagnosis is made.

Diagnostic aspiration is dangerous because of the risk of spilling hydatid fluid and scolices. Anaphylactic phenomena may occur and the risk of secondary cyst formation is present. There is the added danger that the area of dulness which is being aspirated may be caused by an aneurysm of the ascending aorta or of the heart. Marten (1921) withdrew only débris on aspiration of a large pericardial cyst.

Surgical exploration is justified for the diagnosis of a mass which is detected radiologically as associated with the heart and shows only transmitted pulsation. Therefore the diagnosis can never be made with absolute certainty without exploration of the region. Hydatid disease is the most likely diagnosis in the presence of a non-expansile rounded mass associated with the heart, particularly if the wall is calcified, or with the lung sowing described.

The Possibility of Therapy

When hydatid disease of the heart is diagnosed and there is no evidence of inoperable peripheral spread, particularly to brain or lung, surgery offers the only possibility of cure.

Aspiration of the cyst contents, or the injection of formalin is condemned as likely to be highly dangerous in cases in which the cyst communicates with a surface of the heart or part of the bronchial tree. Drainage of the cyst as first performed by Long (1932) offers some hope of cure, while complete surgical removal of the laminated membrane will give a certain cure, provided care has been taken to avoid local spilling of cyst contents at the time.

The best results must be obtained from the treatment of pericardial cysts as there is less likelihood of rupture of the heart as a complication. This latter will be most likely to occur in cysts embedded in the myocardium, because of the thin layer of muscle and adventitia on the inner side of the cyst separating it from the heart chamber. Removal, or even drainage of such a cyst, by lowering the pressure within it, allows the laminated membrane to fall away from the now unsupported inner wall of adventitia which may be ruptured by the normal intracardiac pressure. There is the possibility that even the adventitia is lacking

on the inner side and the laminated membrane is lining the great vascular channel at this point. Hinder (1898) records such a relation of a hydatid cyst to the left bronchus and pulmonary artery, so that fatal hæmorrhage occurred when the cyst was incised and decompressed at operation.

When it is possible, accurate preoperative localization by radiography and electrocardiography will assist surgical therapy.

Zizmor and Szucs (1945) consider that operation is not justified unless symptoms are present, even, as in the case they report, when there is a calcified spherical shadow on the upper border of the heart shadow and a positive Casoni reaction has been obtained. This attitude is difficult to reconcile with our knowledge of the pathology of this disease in which it is seen that nearly all of those affected will die. When the diagnosis is suggested, exploration offers a chance of cure. The operability, that is, possibility of removal without the production of fatal hæmorrhage or aneurysm, may be assessed at the time of operation.

SUMMARY

1. A case is reported of hydatid disease of the pericardium which followed rupture of a primary myocardial cyst and which later ruptured back into the pulmonary artery, producing multiple pulmonary hydatid cysts. Death was due to hæmorrhage from the intrabronchial rupture of one of the pulmonary cysts.

2. Some aspects of the pathology of cardiac hydatid disease are discussed, in particular the route of infestation and the consequences of pericardial rupture.

3. The fate of peripheral hydatid emboli is discussed, especially the failure of many emboli to survive after implantation.

4. The problems of diagnosis and treatment of hydatid disease of the heart and pericardium are considered in the light of modern techniques.

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Proceedings of The Royal Australasian College of Physicians

ANNUAL MEETING, 1952

The Annual Meeting of the College in 1952 was held at Adelaide from May 28 to 31. Sixty-six Fellows and Members attended, representing all States of the Commonwealth and New Zealand.

Scientific Sessions

J. A. R. Miles (Adelaide) opened the first scientific session with a paper entitled " Observations on Virus Encephalitis in South Australia ". He said that at the same time as the epidemic of encephalitis in the Murray Valley in Victoria and New South Wales a few cases of *encephalitis occurred in South Australia*, and a strain of virus similar to that from the Murray Valley was isolated. A serological survey was carried out, use being made of the neutralization test and the complement fixation test (the latter tests were carried out by Mr. D. W. Howes with a mouse brain antigen which he had developed). This survey showed that infection of man and horses had been common in the Murray Valley in South Australia and had occurred to a significant extent throughout the northern agricultural areas. In other parts of the State only occasional " positive " sera were found, but infection of aborigines in the Northern Territory was as common as infection of white men in the Murray Valley. Meteorological data showed that the outbreaks of Australian X-disease in 1917, 1918 and 1925 and the Murray Valley outbreak in 1951 had been associated with widespread exceptionally heavy rainfall in Northern Territory and north Queensland, where in the absence of known epidemics antibodies were found in many human sera. The rainfall in the areas affected by the epidemics had not been so consistent as that in the northern areas, but when there had been an epidemic in the dry areas of New South Wales it had followed heavy rains in the immediately preceding months, which would have left conditions attractive to water birds and suitable for mosquito breeding. The following theory of the natural history of the disease was proposed :

> The virus is a virus of wild birds in which it normally causes a mild non-fatal disease with either a brief or fairly prolonged viræmia. We may hazard a guess that it may be spread between birds either by mites or mosquitoes. In seasons with exceptionally early rains in the north, when birds breed early and second broods are usual, early movements of young birds to the south occur ; many of these birds may be infected and, when they arrive at suitable destinations in the season when mosquitoes and susceptible juvenile locally bred birds are numerous, they initiate an epizootic. When, either by direct flight or through a chain of infection arising from shorter dispersal flights, the birds initiate an epizootic in a more densely settled area, man and his domestic animals may be casually infected. The exact area in which the epidemic occurs will depend on the arrival of infected birds at a time optimal for spread of the disease.

Ewen Downie (Victoria) delivered a paper entitled " Diabetes Mellitus in Association with Lowered Renal Threshold to Glucose " (page 124).

E. G. Saint (Victoria) presented a paper on " The Problem of Chronic Alcoholism ". He said that chronic alcoholism was prevalent in Australia : seventy-eight patients had been comprehensively studied at the Clinical Research Unit of the Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital between 1947 and 1951. A high proportion of patients were of poor intelligence, or were emotionally immature or unstable. The clinical syndromes associated with alcoholism were found to be attributable to a variety of dietary deficiencies, including those of proteins, the vitamin *B complex and iron. Gastritis* with dyspepsia and hæmatemesis, hepatic enlargement with jaundice and ascites, peripheral neuropathy, and encephalopathies were common modes of presentation. Good results were obtained with diet and vitamin treatment whilst patients were in hospital, but the severe difficulties encountered in long-term management were reviewed. It was felt that the management of the alcoholic required the cooperative endeavour of both the physician and the psychiatrist. The study of alcoholism made it clear that future inquiries must inevitably extend into the fields of human genetics and of sociology.

C. G. Bayliss (New South Wales) presented a paper entitled " Cystic Disease of the Lung ". He said that basically lung cysts were bronchogenic or alveolar in origin. Both types might be congenital or acquired, and in both types vital and mechanical factors played a part in causation. Disturbances of growth leading to local hypoplasia resulted in conditions mechanically favourable for the development of congenital cysts. Disturbances of growth might result from inherent defect of the *Anlage* cells, faulty local nutrition and other unknown factors of a vital character. Cysts occurred in the sequestrated lung segment, a somewhat rare developmental anomaly which appeared to result from mechanical interference with the growing bronchial tree by an abnormal blood vessel. Vascular anomalies might be a factor in causation of congenital cysts apart from the sequestrated lung segment. Acquired cysts resulted from partial blockage of a small bronchus, in which a check-valve mechanism developed. The state of the bronchial wall seemed to determine whether the resulting cyst was bronchial or alveolar in type. Metabolic diseases, by interfering with the normal post-natal development of the lungs, might sometimes be a factor in the occurrence of all types of cyst. Cysts in the lung led to symptoms by reason of pressure, by becoming infected and by rupture leading to spontaneous pneumothorax. In bronchogenic cysts carcinoma might originate in the wall. In an infant cystc disease might lead to retarded development. Extensive cystic disease might cause the patient to be a respiratory cripple. Occasionally the presence of lung cysts might be strongly indicated by the history and physical examination. However, X-ray examination was usually necessary to establish the diagnosis : in most cases the diagnosis could be made from the standard film. Bronchography and tomography might be required, and the diagnosis in some cases could be made only after thoracotomy.

Because of the potential hazards, lung cysts should be removed if that was technically possible and no contra-indication existed. In extensive cystic disease of alveolar origin not considered suitable for operation, either because of the widespread nature of the condition or because of the poor general condition of the patient, suction drainage of the Monaldi type might sometimes be employed.

G. C. DE GRUCHY (Victoria) presented a paper on "Auto-Antibodies in Acquired Hæmolytic Anæmia".

W. HAMILTON SMITH (Victoria) discussed "Carbohydrate and other Metabolic Disturbances after Gastrectomy". He said that although the operative treatment of peptic ulcer was usually satisfactory, a small number of patients suffered persistent disabilities after gastrectomy or vagotomy. The most common disability was a liability to attacks of palpitation and weakness after meals. There were two types of such attack: early or "dumping" attacks, which occurred during or immediately after meals, and late attacks, which occurred one and a half to three hours after meals. The cause of the early "dumping" attacks was uncertain; the late attacks were due to hypoglycæmia. Dr. Smith said that, with Dr. Russell Fraser, he had made a study of seventeen patients subject to such attacks, following gastrectomy in thirteen cases, vagotomy in three and gastro-enterostomy *plus* vagotomy in one. An assessment was made of the rate of gastric emptying in these patients and in symptom-free controls by radiological methods and by glucose tolerance tests, and clinical, biochemical and electrocardiographic observations were made during attacks. It was found that early "dumping" attacks were associated with excessively rapid gastric emptying, jejunal hyperperistalsis, tachycardia, a rise in blood pressure, peripheral vasoconstriction, an abnormal fall of serum potassium level and electrocardiographic changes—depression of the *S-T* interval, flattening of the *T* wave, an exaggerated *U* wave and a high peaked *P* wave. These changes were attributed to a release of adrenaline and a shift of potassium, whereby potassium was bound with glycogen in glycogen-storing cells, leading to a deficit of available potassium. The late hypoglycæmic attacks were associated with a rate of gastric emptying no more rapid than that in symptom-free controls. They did show, however, an impaired recovery from induced hypoglycæmia and a post-absorptive hypersecretion of insulin (these assays of plasma insulin were carried out by Dr. J. Bornstein of Melbourne). Some relief of dumping symptoms could be obtained by administration of hexamethonium bromide and a diet of frequent small meals with a minimum of fluid and foods rich in carbohydrate. If disabling dumping symptoms persisted over twelve months, further operation should be undertaken to delay gastric emptying. Hypoglycæmic attacks were usually less disabling and could be aborted by administration of carbohydrate. A high protein, low carbohydrate diet made attacks less severe and less frequent.

R. A. BURSTON (South Australia) discussed "The Effect of Cortisone in Adrenal Insufficiency". He said that the defective diuretic response to ingested water in patients with adrenal insufficiency was present even in spite of adequate replacement therapy with desoxycorticosterone acetate or testosterone. The response was restored to normal by administration of cortisone in doses of 25 milligrammes or more. Cortisone overcame the defect by its direct action on the abnormal renal tubular function.

CLINICAL MEETINGS

Clinical meetings were arranged at the Royal Adelaide Hospital and the Adelaide Children's Hospital.

COLLEGE CEREMONY

The Annual Ceremony of the College was held in the Bonython Hall of the University of Adelaide. It was attended by more than 500 guests, including Fellows and Members and their wives and representatives of medical and other professional organizations in South Australia.

The President, Dr. Alex Murphy, delivered a short address in which he welcomed the visitors to the Ceremony. He said that this was the second occasion on which an Annual General Meeting had been held in Adelaide, and that the College was very happy to meet in a city which still retained something of space and grace. For this Adelaide owed a debt of gratitude to its first surveyor general, Colonel Light, which it had acknowledged with a unique memorial deserving of a visit by all present. He traced the history of the College from the formation of its precursor, the Association of Physicians of Australasia, and explained how its activities were proving of great service both to the public and to the medical profession, thus amply justifying the foresight of its founders. Its roll of almost 650 was a tribute to the value placed upon its Fellowship and Membership. In common with the citizens of Adelaide, the College wished to keep green the memory of its men of vision. One way of doing this was by an Oration in honour of one of those who had played an important part in the foundation of The Royal Australasian College of Physicians.

The President then invited Dr. S. W. Pennycuick, Reader in Chemistry in the University of Adelaide, to deliver the A. E. Mills Oratior for 1952, entitled "The Secret of Living" (*The Medical Journal of Australia*, August 23, 1952).

After the Oration guests were entertained at supper in the Union Refectory.

OFFICE-BEARERS

CONSTITUTION OF COUNCIL

The following is the constitution of Council for the period 1952-1953:

Office-Bearers.

President: Alex P. Murphy.

Vice-Presidents: J. G. Hayden, Guy Lendon, I. M. Allen.

Censor-in-Chief: C. G. McDonald.

Honorary Treasurer: W. P. MacCallum

Honorary Secretary: H. Maynard Rennie

Past President: A. Holmes à Court.

Elected Councillors: Fellows: Sir Charles Blackburn, Clive Fitts, T. M. Greenaway, J. G. Hayden, F. Ray Hone, Bruce Hunt, Alex P. Murphy, Sir Wilberforce Newton, S. A. Smith, Allan S. Walker, Ralph Whishaw, Ian Wood. Members: J. J. Billings and James Isbister.

Co-opted Councillors: W. E. Henley and E. G. Sayers.

Substitute Councillor: Richmond Jeremy.

Executive Committee, 1952-1953. The following members of Council constitute the Executive Committee for the year 1952-1953: Alex Murphy (President), J. G. Hayden, A. Holmes à Court, W. P. MacCallum (Honorary Treasurer), C. G. McDonald, H. Maynard Rennie (Honorary Secretary), S. A. Smith, and Ian Wood (substitute member).

BOARDS OF CENSORS

The Boards of Censors of the College are now constituted as follows:

Australia. C. G. McDonald (Censor-in-Chief), Clive Fitts, T. M. Greenaway, F. Ray Hone, F. Blois Lawton, A. W. Morrow, K. B. Noad.

New Zealand. Professor F. R. Smirk (Senior Censor), I. M. Allen, C. R. Burns, F. L. Landreth, S. L. Ludbrook, E. G. Sayers.

DOMINION AND STATE COMMITTEES (1952–1954)

New South Wales. A. Holmes à Court (Chairman), H. Maynard Rennie (Honorary Secretary), Sir Charles Blackburn, Ruthven Blackburn, Innes Brodziak, W. A. Bye, A. J. Collins, Professor Lorimer Dods, T. M. Greenaway, Bruce Hall, John Halliday, James Isbister, Richmond Jeremy, W. P. MacCallum, C. G. McDonald, A. W. Morrow, K. B. Noad, S. A. Smith, A. J. Hood Stobo, Eric Susman, A. H. Tebbutt, Edgar Thomson, Allan S. Walker, G. C. Willcocks.

Victoria. J. G. Hayden (Chairman), J. E. Clarke (Honorary Secretary), R. M. Biggins, J. J. Billings, M. V. Clarke, C. H. Fitts, J. L. Frew, W. W. S. Johnston, T. E. Lowe, Henry McLorinan, Sir Wilberforce Newton, A. J. M. Sinclair, R. O. Southby, M. Tallent, H. Hume Turnbull, A. E. Rowden White, S. W. Williams and Ian J. Wood.

South Australia. Guy Lendon (Chairman), C. B. Sangster (Honorary Secretary), F. H. Beare, Mark Bonnin, M. E. Chinner, Malcolm Cockburn, Geoffrey de Crespigny, E. F. Gartrell, K. S. Hetzel, Ray Hone, E. Britten Jones, E. McLaughlin.

Queensland. Alex Murphy (Chairman), W. G. Livingstone (Honorary Secretary), P. A. Earnshaw, H. W. Johnson, Harold Love, Professor Ellis Murphy, A. H. Robertson, L. D. Walters.

Western Australia. H. S. Lucraft (Chairman), H. K. Pawsey (Honorary Secretary), J. Gordon Hislop, Bruce Hunt, J. H. Young.

Tasmania. Ralph Whishaw (Chairman), G. Robbie (Honorary Secretary), T. C. Butler, W. Crowther, J. L. Grove, M. W. Fletcher.

New Zealand. Auckland: E. G. Sayers (Chairman), W. E. Henley (Honorary Secretary), Russell Chisholm, Chisholm McDowell. Wellington: Morvyn Williams and I. M. Allen. Christchurch: M. K. Gray. Dunedin: G. R. Kirk.

MEMBERSHIP

Election of Fellows. At the meeting of the General Body of Fellows held on May 29 the following Members were elected to Fellowship of the College: C. G. Bayliss, J. H. Colebatch, K. J. Grice and W. E. King.

Admission of Members. Prior to the meeting of the Council examinations for Membership were held in both Australia and New Zealand. The following successful candidates were admitted by the President to the Membership of the College: J. L. Allsop, A. L. Anderson, G. E. Bauer, D. A. Ballantyne, B. P. Billington, J. V. Cable, R. G. Dreadon, A. A. Ferris, J. J. Fitzwater, A. J. Goble, C. Gresson, P. F. Hall, D. A. Henderson, K. H. Holdgate, C. W. Howden, J. D. Hunter, I. R. Mackay, T. G. Maddison, J. W. Perry, D. W. Piper, V. E. Sampson, G. Selby, B. C. Sinclair-Smith, I. D. Thomas, A. R. Tink, D. Tomlinson, A. S. Turner, R. H. Vines, C. E. Watson.

Membership Roll. The College now has a roll of 291 Fellows and 382 Members.

Obituary. The Council records with regret the death of Dr. F. J. Niall of Victoria and Dr. F. Guy Griffiths of New South Wales, who were Fellows of the College, and Dr. George Reid of Victoria, who was a Member of the College.

GENERAL

Travelling Scholarship in Medicine and the Allied Sciences. The Travelling Scholarship in Medicine and the Allied Sciences for 1952 was awarded to A. Kerr Grant of South Australia.

Research Activities. In accordance with the recommendations of the Research Advisory Committee, Council has made grants to the following: (i) Dr. C. J. McRae (Victoria) to aid his work on "The Exercise Test in the Diagnosis of Cardiac Pain" at the London Hospital. (ii) Dr. W. Hamilton Smith (Victoria) to aid his work on "Metabolism in Patients following Gastrectomy" at St. Vincent's Hospital, Melbourne.

Representation of New Zealand on Council. At an Extraordinary General Meeting held on May 29 an amendment to the Articles of Association was adopted. This amendment provides for the representation of New Zealand upon the Council by two elected Fellows in addition to the Dominion Vice-President who is *ex officio* a Councillor. After this amendment is approved by His Excellency the Governor and the Executive Council, the first election will be held at the time of the Annual Meeting in 1953.

Future Meetings of the College. The Annual Meeting in 1953 will be held in Hobart in the third week of March, and the Ordinary Meeting of that year will be held in Brisbane. In 1954 the Annual Meeting will be held in Melbourne.

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